# TREATMENT OF SHOCK IN THE BURNED CHILD

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THIS review of the resuscitation of burned children under 12 analyses the current practice in the Royal Edinburgh Hospital for Sick Children, and describes the early response of children so treated.

81 children, whose intravenous resuscitation was supervised by us, were admitted during the five years 1955–59.

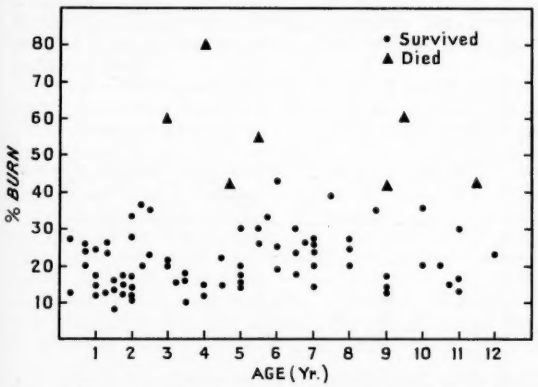


**Fig. 1—Distribution of patients according to age and size of burn.**

The distribution in terms of age, percentage of body surface burned, and ultimate mortality, is shown in fig. 1. The extent of burn is estimated with Lund and Browder's (1944) modification of Berkow's surface-area chart, erythema being excluded from the sum. Resuscitation is undertaken whenever needed, however large the burn.

Though most burning accidents in this area occur reasonably near the hospital, children may be transferred for primary treatment from distances up to 60 miles. If possible, intravenous treatment is begun before transit whenever it is thought that more than three hours may elapse before the child reaches hospital. In this series, the average delay from burn to the start of resuscitation has been two and a half hours—the longest single interval was five and three-quarter hours. In young children every effort must be made to reduce the time between injury and treatment, both before and after admission.

## Clinical Routine

Gentleness must be combined with speed.

### THE FIRST PHASE

*Weight.*—The child's weight is recorded on a stretcher-scale on arrival at the ward. This gives a quick reading with the least handling. Individual weighing is desirable, because many of these children are underweight. The child is transferred from the scale to a rug-canvas open-mesh frame, covered with a layer of Gamgee tissue (fig. 2).

*Assessment.*—If shock is evident, a rapid intravenous transfusion of plasma is given, and accurate assessment of the extent of the burn is postponed until the clinical state has improved. If there is no shock, a detailed chart of the extent of the burn is made. A baby requires intravenous therapy for a burn of about 8%, but an older child may tolerate a burn of up to 15% without transfusion. Whenever greater areas are involved, a transfusion of plasma is started. Otherwise treatment at first is with oral fluids alone though sometimes an intravenous transfusion will be required later. Pre-existing illness and undernourishment will increase the severity of shock, as will delay in starting treatment or careless handling.

*Transfusion routine.*—Continuous transfusion for two days or more is best carried out through a polyethylene cannula in an arm vein. Access to the vein can be through burned skin. The internal saphenous vein at the ankle is a poor route for a fast or a prolonged transfusion. Reconstituted dried plasma is the main fluid used. In the extensive deep burn, whole blood is included. No other electrolyte-containing solutions are used as a routine. The rate at which the plasma is transfused depends on the severity of the shock, and is rapid until shock is controlled. Thereafter the transfusion is maintained at a rate which will prevent shock redeveloping. If plasma is being given to avert shock, a slower rate is used. The duration of the plasma transfusion depends on the extent of the burn. A slow infusion of 5% dextrose in water is continued for several hours after the plasma has been stopped, to avoid another " cut-down " in the rare instance where further plasma is required.

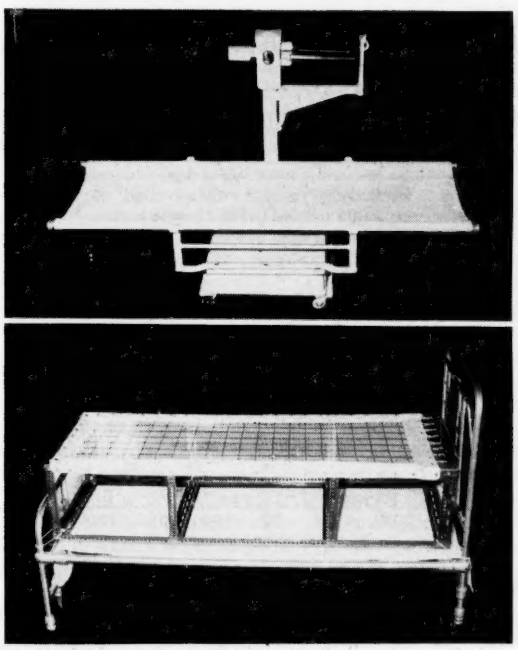

**Fig. 2—Stretcher-weighing scale and open-mesh nursing frame.**

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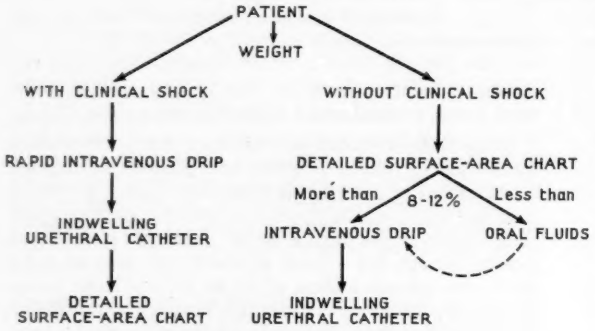


**Fig. 3—Outline of procedure on admission.**

*Catheterisation.*—A Foley urethral catheter, size 8–12 French gauge, is passed in all children receiving intravenous therapy, and the volume of urine is measured frequently.

Fig. 3 summarises the early phase of clinical routine.

### THE SECOND PHASE

*Control of resuscitation.*—Repeated and frequent examination of the child by the same attendant is the guiding principle in the control of treatment. Assessment is continuous at first; and thereafter at increasing intervals, provided the response is satisfactory. The transfusion is adjusted according to the child's general state, peripheral circulation, and hourly urine output.

*Analgesia.*—Diamorphine hydrochloride (heroin) is given intravenously in doses varying between gr. $^1/_{96}$ (0·625 mg.) at ages 0–2 years, and gr. $^1/_{48}$ (1·25 mg.) at ages 2–12. Heroin is given partly for the relief of pain (especially in the superficial injury) and partly for its general calming action. The restlessness of uncontrolled shock must not be mistaken for the distress of unrelieved pain.

*Oral intake.*—Nothing is given by mouth until shock is controlled, or if a general anæsthetic is contemplated for the purpose of dressing the burn. Apart from these contraindications, water is given by mouth in amounts that vary from 10 to 30 ml. per hour, according to age. These quantities are gradually increased to 45 to 75 ml. per hour by the end of the second day. On this regimen, vomiting is unusual. Children may vomit either when the oral intake is excessive or when the intravenous colloid is insufficient. Thirst at this stage is not an indication to increase the water intake.

*Local treatment.*—At first the child is covered with a single layer of Gamgee tissue, and the cleaning of the burn and the application of any formal dressing are delayed until the circulatory state has remained satisfactory for at least two hours. The choice of intravenous heroin analgesia or of general anæsthesia depends on the anticipated difficulty of the procedure. Signs of a burn of the respiratory tract are a contraindication to general anæsthesia, unless a tracheotomy is to be done.

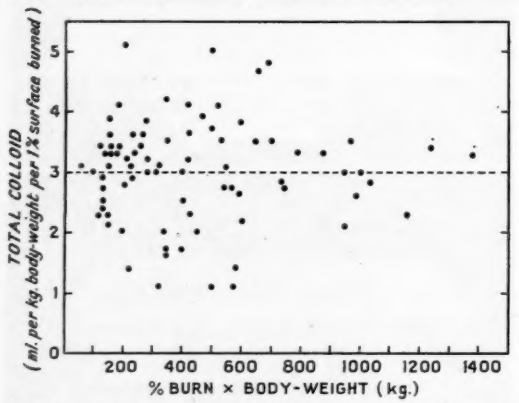


**Fig. 4—The transfusion of each child is expressed as ml. per kg. body-weight per 1% of body surface burned.**

The scale on the horizontal axis is the product of the percentage body surface burned and the body-weight.

The dotted line represents the average colloid transfusion for the series.

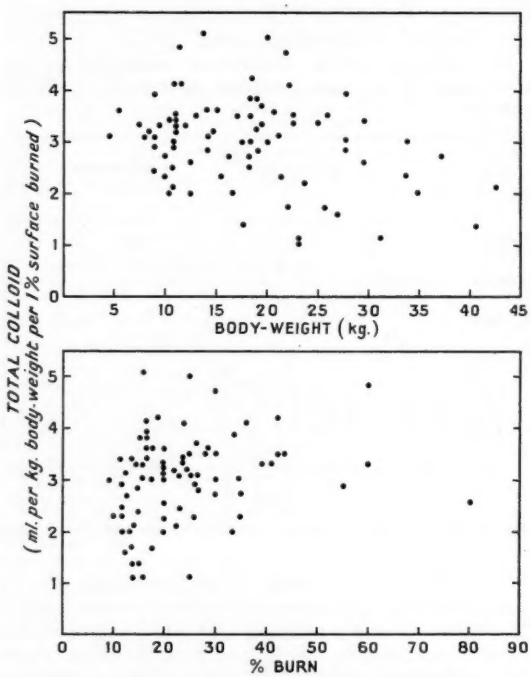


**Fig. 5—The transfusion of each child is expressed as ml. per kg. body-weight per 1% of body surface burned, and considered separately in relation to body-weight and percentage burn.**

## Discussion

*Choice of fluids.*—Analyses have been made of the protein and sodium content of the reconstituted dried plasma given. The protein content averages 5·4 g. per 100 ml. This corresponds to the levels found in lymph and in the œdema fluid after deep burns (Cope et al. 1949). Additional electrolyte solutions would change these levels by dilution and were therefore excluded. The mean sodium content of the plasma is 150 mEq. per litre. This is slightly higher than the normal extracellular sodium value, owing to the added anticoagulant, but is comparable to normal saline. In the deep burn, whole blood was given in amounts judged adequate to replace a deficit of 10–20% of the red-cell volume. Isotope studies, both human and experimental, indicate that the red-cell loss is of this order (Davies and Topley 1956, Raker and Rovit 1954).

*Amount.*—This was determined in all cases by the clinical needs of the child. A rough estimate of the volume likely to be required is given by a modification of Evans' formula (Evans et al. 1952). In this modification the total volume is unaltered but

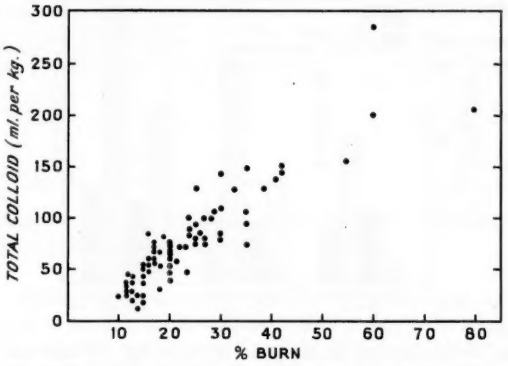


**Fig. 6—The total colloid transfusion in ml. per kg. body-weight is charted against percentage body surface burned.**

is supplied solely by plasma and blood. The total expected volume, V, to be given during the period of shock, is given by: V(ml.)=kWB, where k is a numerical factor (usually 3), W is the body-weight in kilogrammes, and B is the area of the burn, expressed as a percentage of the total body-area. No attempt is made to give specified fractions of this amount in specified periods of time.

*Control.*—The urine volume is measured hourly. Hypotension stops the formation of urine. In the severely burned patient, standard methods of determining blood-pressure are inapplicable, and it is in this group that urine-volume measurement is invaluable. Definite oliguria or anuria, associated with hypotension, is an indication for rapid colloid transfusion. In some children with deep burns, restoration of adequate circulation does not affect the oliguria. In our experience, this group have hæmoglobinæmia and hæmoglobinuria; and, without specific treatment, renal failure will be progressive. As soon as an adequate circulation is restored, 1 g. mannitol per kg. body-weight in a 15% solution is infused over ten to fifteen minutes. A transitory solute-diuresis is the indication of effective treatment (Dudley et al. 1957). This syndrome must be sought, recognised, and treated with a sense of urgency: a few hours' delay renders the solute diuretic ineffective.

Serial hæmoglobin and hæmatocrit estimations have not been performed. The repeated disturbance to the child, the difficulty of interpretation when the burn is deep, and the ignorance of the level before injury, restrict their value as diagnostic aids. Significant elevation in their levels represents an existing deficit, and treatment based on this, being retrospective, is always in arrears.

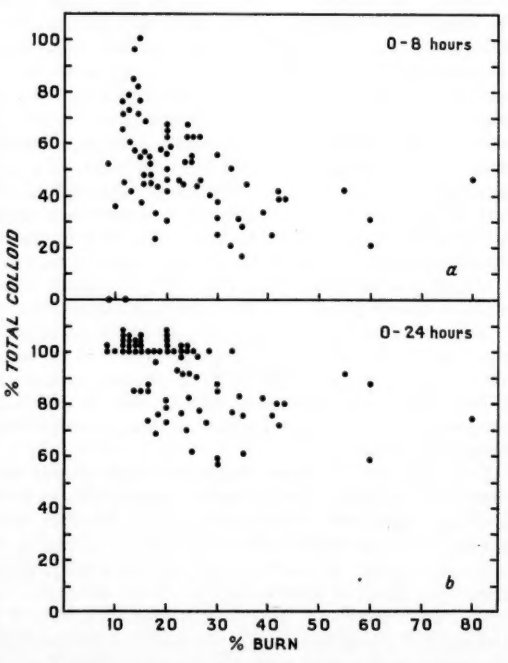


**Fig. 7—The proportion of the total colloid transfused. (a) First eight hours after burn, and (b) first twenty-four hours after burn.**

### Review of Cases

In children, fluid loss and, therefore, fluid replacement must be related to the size of the patient and to the extent of the burn. In most formulæ for estimating the volume needed, fear of overloading the circulation has imposed an upper limit whereby patients with burns of over 50% have their fluid requirement calculated at the 50% level. We imposed no such arbitrary limit, and the figures in the subsequent charts relate in each instance to the actual area burned.

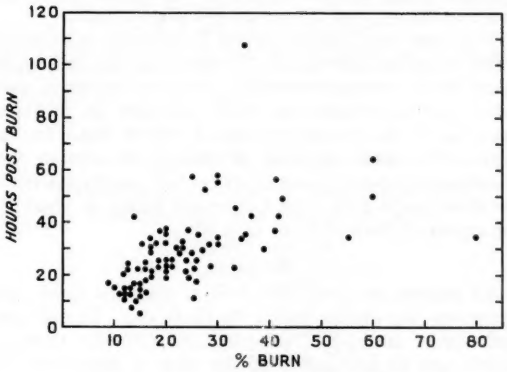


**Fig. 8—Duration of colloid transfusion.**

Analysis of the total amounts transfused into each child was made. Reduction to 1% burn and body-weight gave the actual numerical factor in each case. These values are shown in fig. 4. While the majority of readings are between 2 and 4, there is an individual variation between 1 and 5. The average for the series is 3. Though this average corresponds exactly to the expected figure, it must be emphasised that the individual range is too wide to substitute the use of a formula for careful clinical control. In fig. 5, the same numerical factor is related separately to body-weight and to percentage burn. The constant decreases slightly in the heavier child, possibly because of the changing ratio of surface area to weight in the growing child. Observations on adolescents, not included in this series, confirm this trend.

Fig. 6 shows that the amount of total colloid transfused increases with the size of the burn. At any one size of burn, however, the individual variation in the amount of colloid transfused remains. The relation of colloid transfusion to size of burn is not linear. Although there are few patients with burns of over 40%, their total colloid transfusions are lower than a direct linear relationship would predict. The satisfactory response to treatment of this group with extensive burns suggests that the fluid loss also follows the same trend. The findings of Artz and Reiss (1957) in a large series of extensive burns support this hypothesis.

Fluid loss is greatest in the first eight hours after burn, and continues at a diminished rate for the next twenty-four to forty-eight hours. Infusion designed to parallel this loss should show the same changes in rate. Fig. 7a shows the

amount given to each child in the first eight-hour period, expressed as a percentage of the whole infusion.

In burns of less than 20% of the body surface, 59% of the total was the average transfused, while for burns of over 20%, the corresponding figure was 43%. In the first twenty-four hours after burn (fig. 7b) the average transfused for burns of 20% or less was 96%; and 85% of the total colloid was transfused in those with burns of over 20%. Percentages of 33 and 66 have been suggested (Evans et al. 1952, Reiss et al. 1953, Kyle and Wallace 1951) for the eight-hour and twenty-four hour periods respectively, but the child makes a quicker recovery and maintains a more satisfactory circulatory state when the rate of transfusion is more rapid.

The higher transfusion-rates employed in the treatment of these children have not produced any evidence of temporary overloading of the circulation.

The child admitted late requires a rapid transfusion to begin with, but this delay does not necessitate larger total amounts being transfused, either during the first eight hours or throughout the period of resuscitation.

The time over which colloid transfusion is required varies considerably (fig. 8). Transfusion for forty-eight hours is not always necessary. In many instances, provided the transfusion has been adequate in rate and amount, it can be safely stopped before this. In our series, the usual duration of colloid transfusion was twenty-four hours for burns up to 20%, thirty-six hours for those up to 30%, and forty-eight hours or more for the extensive burn of more than 30%.

## Results

All patients survived the phase of oligæmic shock, and there were no deaths before the ninth day. In the great majority of cases, a satisfactory response was obtained within one to four hours of the start of treatment. In isolated instances clinical response was sluggish, though it was satisfactory in four to eight hours. In some, the reason for this was not apparent; in others, it was associated with prior illness, undernourishment, or excessive analgesia, before admission. The size of the burn was not a contributory factor.

In 2 cases, both suffering from extensive deep scalds (60% and 35%), a poor clinical response to rapid plasma-transfusion was associated with the development of tetany. Both these children had necessarily received a more rapid plasma transfusion than usual. A striking clinical improvement, as well as relief of the tetany, followed intravenous administration of 2 g. calcium gluconate in the first child, and 1 g. in the second.

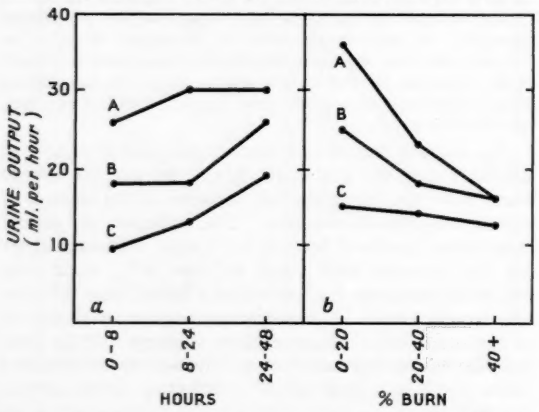


**Fig. 9—Alterations in urine output according to time after burn (a), and to size of burn (b).**

Line A—Weight-group 25 kg. and over (age 9 and over).
Line B—Weight-group 12 to 25 kg. (age 2 to 9).
Line C—Weight-group 0 to 12 kg. (age 0 to 2).

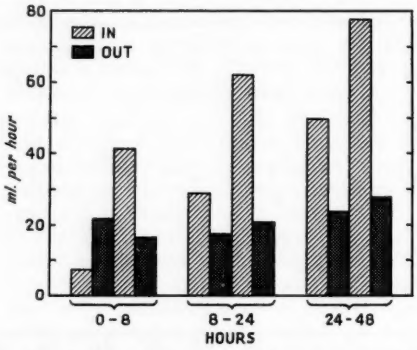


**Fig. 10—Comparison of the effects of low-water and high-water intakes on urine output during the first forty-eight hours after burn in children aged 2 to 9.**

Hypotension, cardiac dysrhythmias, and tetany are recognised features of citrate intoxication (Moore 1959), and we believe that the poor response to resuscitation in these children may well have been aggravated by excessive citrate load.

In two-thirds of the total, local treatment was undertaken within ten hours of injury. Reversion to a state of shock did not occur, although this is a danger unless handling is gentle and the transfusion-rate closely supervised. In 3 cases definitive local treatment was delayed for 40, 40, and 46 hours. Earlier local treatment was thought to carry a serious risk. Nursing on a mesh frame and the administration of a systemic antibiotic minimised the possible objection to such a delay.

When urine volume is used as an important index in control of resuscitation, correct interpretation depends on a knowledge of what urinary volumes may be expected. In health, this volume will vary with the size of the child. To assess the influence of this, and other factors, after burning injury, the children were divided into three groups according to weight. In fig. 9a the mean urine output per hour was averaged for each weight-group and considered in relation to the time since the burn. It will be seen that age, as expected, influences volume. Volume also increases during the first forty-eight hours. Though hypotension is the basis of oliguria, before and at the start of resuscitation, correction of this does not result in "normal values" being attained. Increase in colloid transfusion-rate in an effort to obtain a "normal output" is neither necessary nor desirable. Where colloid transfusion is closely allied to clinical needs, no gross fluctuations in urine output are observed. In fig. 9b, the mean urine output per hour over forty-eight hours in the same three weight-groups is considered in relation to the size of the burn. The output is seen to fall as the burn increases in size, a sequence which becomes more obvious in the older child.

The influence of water intake on urine output was studied in the largest group, whose weight ranged from 12–25 kg. (ages 2–9). The children, 35 in number, were separated into an upper and a lower group according to their water intake. In the three periods, the average urine output per hour of each group is shown alongside the average water intake per hour for that group (fig. 10). It is obvious that a large increase in the water intake has little or no effect on the urine output at this stage. Antidiuresis, decreasing with the passage of time, and increasing with

CASE-FATALITY

| Case | Age | Burn (percentage of body area) | Day of death |
|---|---|---|---|
| 1 | 4 | 80 | 35 |
| 2 | 9 | 41 | 36 |
| 3 | 11 | 42 | 61 |
| 4 | 5 | 55 | 10 |
| 5 | 3 | 60 | 10 |
| 6 | 9 | 60 | 9 |
| 7 | 4 | 42 | 9 |

the severity of the injury, offers the most likely explanation for the foregoing observations.

### Mortality

7 patients, whose burns were both extensive and deep, died. 3 patients (cases 1, 2, and 3) died at thirty-five, thirty-six, and sixty-one days respectively. Widespread infection was found at necropsy. 2 children, who were admitted late in severe circulatory failure, died on the tenth day. In one of these (case 4) renal damage in association with gross hæmoglobinuria proved fatal. Necropsy in the other (case 5) revealed no major organic failure, but this child had been in extremis on admission. 2 patients died on the ninth day; 1 (case 6) had multiple visceral infarcts, following a high-tension electrical burn; the other (case 7), showed partial renal recovery after a severe hæmoglobinuria treated with mannitol infusion. Severe hypernatræmia developed; but its recognition was delayed, and its treatment inadequate.

### Conclusions

In children, the shock produced by any size of surface burn—no matter how great—can be controlled by early energetic resuscitation. Ultimate recovery after deep burns of more than half the body surface may have to await the solution of longterm homograft survival.

Plasma and blood are, by themselves, efficient in controlling burn shock. The omission of normal saline and similar fluids is without disadvantage, and simplifies the régime.

An estimate, in advance, of the likely total colloid need is of help. For this purpose, a figure of 3 ml. of colloid per kg. body-weight per 1% of body surface burned has been found useful where, as in childhood, the size of the patient and the burn vary widely. The value of such a calculation lies in the protection it affords against gross errors being made in transfused volumes. Because of wide deviations from this value met in our series, rigid adherence to an estimated volume is to be condemned.

When the size of the child, the size of the burn, and the time after injury are taken into account, the volumes of urine obtained by catheter are of great significance.

Frequent observation at the bedside remains the foundation of successful resuscitation.

### Summary

A routine for the resuscitation of burned children is described.

If a burned child is shocked, a transfusion of reconstituted dried plasma is given at once. If there is no shock, a transfusion is started if the extent of the burn is more than 8% of the body surface for a baby or 15% for an older child. Whole blood is added if the burn is both extensive and deep.

The burn is not dressed until the child's circulatory state has remained satisfactory for at least two hours. Intravenous diamorphine hydrochloride is given for the relief of pain.

Plasma and blood, by themselves, have been effective in controlling shock and in restoring fluid loss. The total amount of colloid needed is about 3 ml. per kg. body-weight per 1% of body surface burned. This is no more than a rough estimate, and not one to be adhered to rigidly. The output of urine is of great value in assessing progress, and in determining the volume of fluid to be transfused. Successful resuscitation is based on careful clinical observation.

The resuscitation of 81 children by this method is reviewed.

Grateful acknowledgment is made to Mr. A. B. Wallace, in whose ward these cases were treated. We are greatly indebted to the nursing staff, especially to Sister P. Robbie and Sister E. Redpath, whose care and attention to detail made this study possible.

REFERENCES

Artz, C. P., Reiss, E. (1957) The Treatment of Burns. Philadelphia.
Cope, O., Graham, G. B., Mixter, G., Ball, M. R. (1949) *Arch. Surg.* **59**, 1015.
Davies, J., Topley, E. (1956) *Clin. Sci.* **15**, 135.
Dudley, H. A. F., Batchelor, A. D. R., Sutherland, A. B. (1957) *Brit. J. plast. Surg.* **9**, 275.
Evans, E. R., Purnell, O. J., Robinett, P. W., Batchelor, A., Martin, M. (1952) *Ann. Surg.* **135**, 804.
Kyle, M. J., Wallace, A. B. (1951) *Brit. J. plast. Surg.* **3**, 194.
Lund, C. C., Browder, N. C. (1944) *Surg. Gynec. Obstet.* **79**, 352.
Moore, F. D. (1959) Metabolic Care of the Surgical Patient. Philadelphia.
Raker, J. W., Rovit, R. L. (1954) *Surg. Gynec. Obstet.* **98**, 169.
Reiss, E., Stirman, J. A., Artz, C. P., Davies, J. H., Amspacher, W. H. (1953) *J. Amer. med. Ass.* **152**, 1309.

## MULTIPLE SCLEROSIS

### Trials of Maintenance Treatment with Prednisolone and Soluble Aspirin

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ONE widely discussed hypothesis of multiple sclerosis (Ferraro 1958) is that the essential lesion is an allergic inflammation of the mesodermal vascular ground substance of the central nervous system, arising primarily around the smaller veins of the neuraxis. In this view the characteristic demyelination of the established disease is an epiphenomenon, and initiation of the whole process is ascribed to a pathological deviation of immune mechanisms, possibly excited by some form of antecedent infection. This hypothesis is speculative and derives chiefly from the study of acute nervous diseases provoked in laboratory animals by injecting brain emulsions—the relation of which to human multiple sclerosis is uncertain. Relevant clinical considerations have been reviewed (Miller and Schapira 1959). The most that can be said at present is that other existing hypotheses of ætiology and pathogenesis appear to hold even less promise, and that Ferraro's theory furnishes at any rate a point of departure for further clinical and pathological studies.

This paper presents the results of the first of a series of therapeutic trials. These have been planned with more hope of furnishing further evidence about the nature of multiple sclerosis than of offering anything in the way of a " cure ". We aim to test the allergic hypothesis of multiple sclerosis by observing the effects on the natural history of the disease of drugs which are believed to influence the course of allergic inflammation.

## Method

Eighty-six patients living on Tyneside, who were moderately disabled by multiple sclerosis, were admitted to the trial. Prednisolone tablets of 5 mg., calcium aspirin (' Solprin ') tablets of gr. 6, and dummy (lactate) tablets were used. The initial dosage of prednisolone was 15 mg. per day, but after 8 months this was uniformly reduced to 10 mg. daily because of the risk of side-effects. The patients in the other two groups were given either a corresponding number of dummy tablets or nine solprin tablets (gr. 54) daily. The treatment of all patients began within 10 weeks in the winter of 1958, and was continued for 18 months.

On admission to the trial, each patient was randomly allocated to one of the three treatment groups, and the initial routine was continued unchanged throughout. Seven patients were removed in the course of the trial. One patient on dummy tablets stopped taking them, and three patients having solprin and one having prednisolone failed to take their tablets regularly. An independent observer unconnected with the trial, who examined the patients receiving prednisolone at 3-monthly intervals to detect toxic effects, found it necessary to remove two further patients from the trial because of rising blood-pressure. We do not think these seven patients defaulted because of the progress of their multiple sclerosis. Accordingly they can be excluded from the analysis without imparting a bias in favour of any drug.

## Basis of Assessment

Relevant details of the composition of the three groups of patients are set out in table I. The " dummy " group contained rather more men than the two groups which received active treatment, but this is not statistically significant. The ages of

TABLE I—COMPARISON OF GROUPS BEFORE TREATMENT

| — | Treatment group | | |
|---|---|---|---|
| | Dummy | Solprin | Prednisolone |
| No. of patients | 29 | 24 | 26 |
| Males | 14 | 9 | 9 |
| Females | 15 | 15 | 17 |
| Mean age (yr.) | 33·3 | 32·4 | 33·0 |
| Mean duration of disease (yr.) | 12·7 | 11·9 | 10·4 |
| Recent course of the disease: | | | |
| Slowly progressive | 20 | 13 | 16 |
| Fluctuant | 8 | 9 | 8 |
| Rapidly progressive | 1 | 2 | 2 |
| Previous medication | 2 | 4 | 6 |
| Average severity (Alexander) | 200·0 | 182·2 | 174·9 |
| Functional grade (see text): | | | |
| II | .. | 1 | .. |
| III | 20 | 16 | 19 |
| IV | 9 | 7 | 7 |

the groups were very similar, all being about 33. The mean duration of the disease was 12·7 years in the dummy group, and 11·9 and 10·4 years in the treatment groups.

*Previous Course*

The course of multiple sclerosis before the trial was classified as slowly progressive, fluctuant with exacerbations and remissions, or rapidly progressive. In the dummy group there were twenty patients in whom the disease was slowly progressive, eight in whom it had progressed by exacerbations and remissions, and one rapidly progressive case. The solprin group comprised thirteen slowly progressive, nine exacerbation-remission, and two rapidly progressive cases. The corresponding figures for the prednisolone group were sixteen, eight, and two.

*Previous Therapy*

Two patients on dummy tablets, four on solprin, and six on prednisolone had received previous medication, usually with vitamin $B_{12}$ or some form of arsenic. No patient who had been so treated during the preceding 12 months was included in the trial.

TABLE II—COMPARISON OF GROUPS AFTER TREATMENT

| — | Treatment group | | |
|---|---|---|---|
| | Dummy | Solprin | Prednisolone |
| Average change in Alexander score: | | | |
| From onset to 6 mos. | 11·4 | −1·0 | 6·0 |
| From onset to 18 mos. | 26·7 | 9·8 | 30·2 |
| Functional grades at 6 mos.: | | | |
| II | .. | 1 | .. |
| III | 19 | 16 | 20 |
| IV | 10 | 7 | 6 |
| Functional grades at 18 mos.: | | | |
| II | .. | .. | 1 |
| III | 16 | 15 | 16 |
| IV | 12 | 9 | 8 |
| VI | 1 | .. | 1 |
| Acute exacerbations during trial | 5 | 8 | 6 |
| New symptoms | 13 | 10 | 8 |
| New signs | 19 | 17 | 21 |
| Patients' own assessment at 18 mos.: | | | |
| Better | 3 | 5 | 3 |
| No change | 13 | 11 | 10 |
| Deteriorated | 13 | 8 | 13 |

*Clinical Assessment*

Each patient was examined before treatment began, and again after 6 and 18 months. The clinical assessment was recorded in terms of Alexander's (1958) numerical scoring system, in which each neurological sign is given a numerical value, and improvement or deterioration is indicated by a reduction or increase in the total score recorded at successive examinations.

The functional grade of the patients was also recorded at each examination. Patients were classified as follows: grade I—symptom-free; grade II—symptoms, but activities unrestricted; grade III—moderately restricted; grade IV—much restricted; grade V—confined to home; grade VI—immobile at home; grade VII—bedridden.

At the 6 and 18 month examinations specific inquiry was made about any acute exacerbations or new symptoms experienced. The patients were also asked if they thought their condition had improved, deteriorated, or remained unchanged.

The average scores in Alexander's system for the three groups at the outset of treatment were 200·0 (dummy), 186·2 (solprin), and 174·9 (prednisolone): analysis of variance shows that these averages did not differ significantly (variance ratio = 0·62). Nor was there any significant difference in the functional grading of the groups before treatment. We therefore conclude that random allocation of the patients had produced groups comparable in all the above respects.

## Comparison after Treatment

*Alexander Scores*

To eliminate the effect of the considerable variation between the Alexander scores of patients on admission to the trial, analysis is based on the difference between each patient's score at 6 and 18 months, and his initial scoring. A positive difference indicates deterioration, a negative difference an improvement, in the patient's condition. Disability was assessed and scored by an observer who was unaware of the patient's treatment group at the time of examination.

The average differences are presented in table II. There was relatively little change in the average grading at the end of the first 6 months' treatment. After 18 months the patients on solprin had deteriorated by 9·8 points, and the prednisolone patients by 30·2 points, as compared with an average deterioration of 26·7 points in the control group receiving dummy tablets. The standard error of the difference between the mean deterioration for either treatment and that for the dummy is 14·5. Thus neither treatment is significantly better than the dummy treatment.

An alternative way of assessing the results (which was not originally intended) is to test whether each group had deteriorated significantly over the 18 months. Using this basis, we find that the 9·8 points of deterioration for solprin patients is not significant, whereas the 26·7 and 30·2 average deterioration scores in the dummy and prednisolone groups both represent significant worsening. This second method of analysis cannot be regarded as providing firm evidence that solprin retards

deterioration in multiple sclerosis, but we feel that the effect of this drug merits further investigation.

*Other Features*

*Functional grades.*—Comparison of tables I and II shows that there were very few changes in the functional gradings in the course of the trial. During the 18 months' observation a few patients in each group deteriorated enough to warrant a change of grading, but there was no significant difference between the three groups in this respect.

*Acute exacerbations.*—There were five acute exacerbations in the dummy group, eight in the solprin group, and six in the prednisolone group.

*New symptoms and signs.*—During the trial, thirteen new symptoms and nineteen new signs appeared in patients taking dummy tablets. The solprin patients developed ten new symptoms and seventeen new signs, and the prednisolone group eight new symptoms and twenty-one new signs.

*Patients' own assessments.*—At 6 months most patients in each group thought that their condition was unchanged. At 18 months, opinions within each group were equally divided between " no change of status " and " definite deterioration ".

There was no statistical difference among the three groups between the numbers of acute exacerbations, nor between the numbers of new symptoms and signs, nor between the patients' own assessments of progress.

## Discussion

The adrenal steroids, apart from their less specific effect in suppressing inflammation (Spain et al. 1952), may depress antibody formation (Herbert and de Vries 1949, Overman and Hanan 1953). Both cortisone (Kabat et al. 1952) and salicylates (Good et al. 1949) afford some protection against experimental " allergic " encephalitis, though this action is possibly mediated chiefly through the adrenal cortex (Woodbury 1958). If antigen-antibody reactions play a part in provoking acute exacerbations of multiple sclerosis or in the pathogenetic mechanisms involved in the slow extension of the chronic lesions of the established disease, it would be not unreasonable to hope that either prednisolone or solprin might retard its clinical progression.

In this connection the observations described above afford little encouragement. The appearance of acute exacerbations, new symptoms, and new signs with almost equal frequency in all three treatment groups suggests that the activity of the disease continued uninfluenced by either prednisolone or solprin in the dosage employed, and there is no positive evidence in favour of the role of allergic mechanisms in its pathogenesis. The progression of chronic disablement was not retarded by the administration of prednisolone in the amount used, which is probably as much as could be safely given during an extended period. With solprin also there was no statistically significant difference between treated and control cases; nevertheless, the condition of the patients taking solprin did not deteriorate significantly during the 18 months' treatment. We have not shown that solprin retards the progression of multiple sclerosis, but our findings do not exclude this possibility, which will be followed up in a further long-term trial.

The problems of assessing the results of treatment in multiple sclerosis, which are notorious, have deterred most clinicians from using methods of control, other than those which are merely historical or even more indirect, to measure their therapeutic observations. Nevertheless the polymorphism and strikingly variable natural history of this disease render objective trial especially important. The observations described above show that valid methods of control can be used in this field, and they provide one possible model for subsequent trials.

We wish to thank Dr. Andrew Lenman, Dr. Peter Leyburn, Dr. Kurt Schapira, and Mrs. D. Weightman for clinical and statistical help with the trial; the North-East Multiple Sclerosis Trust, and Messrs. Reckitt & Colman for substantial financial assistance; and the latter company and Boots Pure Drug Co. for providing the drugs.

REFERENCES

Alexander, L., Berkeley, A. W., Alexander, A. M. (1958) *J. Amer. med. Ass.* **166**, 1943.
Ferraro, A. (1958) *J. Neuropath.* **17**, 278.
Good, R. A., Campbell, B., Good, T. (1949) *Proc. Soc. exp. Biol., N.Y.* **72**, 341.
Herbert, P. H., de Vries, J. A. (1949) *Endocrinology*, **44**, 259.
Kabat, E. A., Wolf, A., Bezer, A. E. (1952) *J. Immunol.* **68**, 265.
Miller, H., Schapira, K. (1959) *Brit. med. J.* i, 737, 811.
Overman, J. R., Hanan, R. (1953) *Proc. Soc. exp. Biol., N.Y.* **82**, 427.
Spain, D. M., Molomut, N., Haber, A. (1952) *J. Lab. clin. Med.* **39**, 383.
Woodbury, D. M. (1958) *Pharmacol. Rev.* **10**, 328.

# OPTIMUM TIME FOR DIALYSIS IN ACUTE REVERSIBLE RENAL FAILURE

## Description and Value of an Improved Dialyser with Large Surface Area

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THE treatment of acute renal failure, using the artificial kidney if necessary, gives good results except when the lesion follows trauma (surgical or accidental), for in these cases the mortality-rate exceeds 50% (Teschan et al. 1955, Bluemle et al. 1959, Parsons and McCracken 1959, Kiley et al. 1960). Although this high mortality-rate can be attributed to complications, such as sepsis, it also depends on the quicker development of uræmia due to rapid protein breakdown. Using conventional indications for dialysis, and machines of limited efficiency, these patients are uræmic throughout most of their course. On the hypothesis that uræmia plays a part in increasing the complications, and is largely responsible for the high mortality-rate, we directed our attention to controlling it more effectively. The means available are (1) increased efficiency of the artificial kidney, and (2) more frequent dialysis.

The frequency of dialysis is limited by the facilities in the artificial-kidney unit in relation to the number of patients referred for treatment, and the need to perform other diagnostic or therapeutic procedures during the course of renal insufficiency.

We here describe the encouraging results obtained in " surgical " patients, using modifications designed to increase the efficiency of our Kolff-Brigham kidney, and in developing and using a new machine which Usifroid of Paris have made by modifying their Necker Hospital model according to our suggestions.

## Biochemical Considerations

Merrill et al. (1950) and Wolf et al. (1951) showed that the clearance-rate across the 'Cellophane' membrane in the Kolff-Brigham rotating machine was dependent on the properties of the membrane, the properties of the substances under investigation, the diffusion gradient across the membrane, and the area of the dialysing surface. Whilst they also showed

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that the clearance-rate for pure solutions was influenced considerably by the flow-rate, during hæmodialysis the plasma flow-rate is probably more important than the whole-blood flow-rate because some substances pass across the red-cell membrane slowly (Parsons 1960, Scribner et al. 1960a). The degree of correction is also dependent on the level at the start of dialysis, and on the total body-water, for most waste metabolites seem to be distributed throughout this volume.

The total body-clearance of substances, such as urea, that diffuse rapidly across cell membranes, can usually be forecast fairly accurately, particularly if the rate of protein breakdown during dialysis is taken into consideration. Most machines in current use have a dialysing surface of about 2·0 sq. m.; and, using the formula of Wolf et al. (1951), it can be calculated that a machine of this surface area will reduce a blood-urea-nitrogen (B.U.N.) of 200 mg. per 100 ml. to 45–50 mg. in an average-sized subject treated for six hours when the blood flow-rate is 300 ml. per minute. In practice the fall is less, because measurable quantities of urea continue to be formed during dialysis, and the total body-clearance during hæmodialysis is less than that for pure solutions. Reduction of the B.U.N. from 200 to 60 or 70 mg. per 100 ml. would not be unreasonable. When the rate of protein breakdown is relatively low, and when the renal insufficiency lasts less than fourteen days, limited correction of the uræmic state is probably of no serious consequence, for renal function usually recovers before a second treatment is necessary. But when the protein breakdown is high—causing, say, a daily rise of B.U.N. of 40–50 mg. per 100 ml.—then inadequate correction of the biochemical abnormalities by hæmodialysis can be serious. In these circumstances, frequent dialyses (often at two-day intervals) are required to control adequately the B.U.N.

For substances that diffuse slowly across cell membranes, the whole-body clearance-rate is less, and (more important) is not proportional to the removal of urea. For instance, we found that the amount of urea removed from a patient decreased considerably towards the end of a six-hour dialysis as the plasma level reached more normal values. On the other hand, the amount of phosphate removed did not fall during the last two hours, and the plasma-phosphate level remained constant, though increased. This, along with other data, suggested that the more slowly diffusible substances were corrected less than the rapidly diffusible substances, such as urea; and the uræmic state was differentially corrected at the end of dialysis (Parsons 1960). Therefore, after dialysis the blood-urea level can no longer be regarded as indicative of the accumulation of other biochemical substances. Naturally, in patients who required more than one dialysis, this differential correction of the uræmic state became more exaggerated each time.

For patients with a high rate of protein breakdown (rise of B.U.N. greater than 30 mg. per 100 ml. per day) we concluded that a machine with a dialysing surface of 2·0 sq. m. could not control the uræmia adequately. We deduced by calculation, and confirmed in practice, that, provided the dialysing surface of the machine was at least 2·8 sq. m., the differential correction of the biochemical abnormalities could be largely prevented by dialysing the patient at lower levels of B.U.N. (120–150 mg. per 100 ml.), or by longer periods of dialysis. The large dialysing area is necessary because the removal of those substances that are dialysed relatively slowly is improved by

TABLE I—CASES WITH RAPID PROTEIN CATABOLISM WHICH WERE DIALYSED FOR ACUTE REVERSIBLE RENAL FAILURE FROM "SURGICAL" CAUSES

| Case no. | Age (yr.) | Sex | Operation | No. of dialyses | Maximum average daily rise of B.U.N. (mg. per 100 ml.) | Recovered | Died | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Day of first fall of B.U.N. | Day of death | Cause of death | Maximum urine output (ml. per 24 hr.) |
| | | | *September, 1956–December, 1958* | | | | | | |
| 1 | 44 | M | Cystoileoplasty | 1 | >30 | .. | 19 | Septicæmia | >2000 |
| 2 | 59 | M | Cystectomy: ureterocolic anastomosis | 2 | 55 | .. | 20 | Paralytic ileus | 1605 |
| 3 | 40 | F | Hysterectomy | 4 | 79 | .. | 26 | Staphylococcal enterocolitis: cerebral abscess | >800 |
| 4 | 67 | M | Transurethral prostatectomy | 2 | 32 | .. | 17 | Staphylococcal enterocolitis | <500 |
| 5 | 58 | M | Aortic valvotomy | 2 | >30 | .. | 13 | Cardiac arrest | <500 |
| 6 | 44 | F | Wertheim's hysterectomy | 1 | >50 | 12 | .. | .. | .. |
| 7 | 32 | M | Appendicectomy: secondary hæmorrhage: laparotomy | 3 | >60 | .. | 10 | Peritonitis | <500 |
| 8 | 55 | M | Partial gastrectomy | 1 | >30 | .. | 12 | Pulmonary and cerebral œdema: bronchopneumonia: wound dehiscence | >1000 |
| 9 | 57 | F | Acute pancreatitis | 1 | >30 | .. | 7 | Acute pancreatitis | <500 |
| 10 | 51 | M | Transurethral prostatectomy | 7 | >60 | .. | 36 | Gastric hæmorrhage: pulmonary abscess | 1500 |
| 11 | 58 | F | Right nephrectomy | 1 | >30 | .. | 6 | Unknown | <500 |
| 12 | 52 | M | Paralytic ileus: laparotomy | 1 | >40 | .. | 7 | Staphylococcal pneumonia and enterocolitis | <500 |
| 13 | 62 | F | Appendicectomy: peritonitis | 3 | >30 | 30 | .. | .. | .. |
| 14 | 20 | M | Partial gastrectomy: secondary hæmorrhage | 3 | 40 | .. | 13 | Hæmoperitoneum: peritonitis | <500 |
| 15 | 70 | F | Choledochotomy: cholecystectomy | 5 | 36 | .. | 44 | ? (necropsy refused) | >1000 |
| 16 | 53 | M | Appendicectomy: peritonitis | 2 | >30 | .. | 18 | Lung abscess eroded bronchial artery | >1000 |
| 17 | 40 | F | Oophorectomy: endometriosis | 1 | >30 | .. | 8 | Pneumonia | <500 |
| | | | *January, 1959–June, 1960* | | | | | | |
| 18 | 73 | M | Suture of perforated duodenal ulcer | 1 | 45 | .. | 8 | Peritonitis: lung abscess | <500 |
| 19 | 32 | M | Partial gastrectomy: subphrenic abscess | 1 | >30 | 8 | . | .. | .. |
| 20 | 55 | M | Left nephrectomy | 4 | 33 | 51 | .. | .. | .. |
| 21 | 50 | F | Stripping left varicose veins: pulmonary embolus | 2 | 48 | 23 | .. | .. | .. |
| 22 | 75 | M | Choledochotomy | 2 | 30 | .. | 10 | Pneumonia | <500 |
| 23 | 68 | F | Bilateral oophorectomy: carcinoma invading colon | 1 | >30 | .. | 7 | Peritonitis: ruptured colon | 1020 |
| 24 | 38 | M | Appendicectomy: peritonitis | 3 | 49 | 19 | .. | .. | .. |
| 25 | 53 | M | Appendicectomy: secondary hæmorrhage and laparotomy | 2 | 38 | 10 | .. | .. | .. |
| 26 | 46 | F | Hysterectomy | 2 | 31 | 14 | .. | .. | .. |
| 27 | 40 | M | Appendicectomy | 1 | >35 | 13 | .. | .. | .. |
| 28 | 40 | F | Hysterectomy: gas-gangrene | 2 | 65 | 11 | .. | .. | .. |
| 29 | 52 | M | Transduodenal choledochotomy: cholecystectomy | 1 | >30 | 7 | .. | .. | .. |
| 30 | 19 | M | Hypophysectomy | 2 | 37 | 19 | .. | .. | .. |
| 31 | 54 | F | McMurray osteotomy | 1 | >30 | 7 | .. | .. | .. |
| 32 | 53 | M | Bilateral herniorrhaphy | 2 | >30 | Onset of renal failure unknown | .. | .. | .. |
| 33 | 26 | F | Mitral valvotomy | 1 | 33 | .. | 6 | Cardiac arrest | 1330 |

increasing the surface area rather than the flow-rate of blood (Parsons and McCracken 1958).

### Clinical Results

The artificial kidney used was the Kolff-Brigham model (Murphy et al. 1952), modified by increasing the dialysing surface to 2·8 sq. m., and the flow-rate of blood to a maximum of 500 ml. per minute (Parsons and McCracken 1958).

From September, 1956, to December, 1958, dialysis was undertaken on the indications of clinical deterioration or a rise in B.U.N. to 200 mg. per 100 ml. Results in the patients who had a high rate of protein catabolism (average daily rise in B.U.N. over 30 mg. per 100 ml.) were very poor. Because of this, and some preliminary results in 1958 (Parsons 1959), we decided to dialyse this group whenever the B.U.N. reached 120–150 mg. per 100 ml. so as to obtain a more balanced reduction of the biochemical abnormalities, as outlined above. This change was made in January, 1959.

For comparison we have chosen patients whose acute renal failure resulted from surgical causes (table I). Only those who had an average daily rise of B.U.N. in excess of 30 mg. per 100 ml. have been included. Between September, 1956, and December, 1958, when dialysis was performed at the onset of clinical deterioration, seventeen such cases were referred for treatment, but only two recovered (11·8%) despite the introduction, in 1957, of barrier-nursing techniques and a larger machine, with a dialysing surface of 2·8 sq. m. The commonest cause of death was sepsis. Since January, 1959, when earlier dialysis was introduced (B.U.N. 120–150 mg. per 100 ml.), sixteen more patients have been treated, and of these twelve have recovered (75%). The average age of these two series was almost identical (50·7 and 48·4 years respectively), and the surgical procedures were similar. Three patients, who died of severe sepsis during the second period were aged 68, 73, and 78; the fourth patient probably died from a blood-transfusion reaction (she had received, in the previous seven days, over 20 pints of blood during and immediately after an open cardiac operation). We are in no doubt that our change in policy to earlier dialysis in these severe cases has been beneficial. The clinical condition of most patients improved dramatically, or remained good throughout the period of renal failure. We witnessed, for the first time, spontaneous resolution of infection.

### The New Machine

The better results with our modified Kolff-Brigham machine warranted the development of a commercial model with similar characteristics. We estimated theoretically that the clearance-rate of the less diffusible substances which accumulate in uræmia would improve further if the dialysing surface was larger than 2·8 sq. m. A surface of 3·2 sq. m. was chosen, because we thought any further increase would have expanded the extracorporeal volume of blood, and the increased circulation-time of blood through the machine would have necessitated giving larger quantities of heparin to prevent clotting.

The Kolff rotating-type kidney was preferred because (1) the dialysing surface can be reduced to any desired size, for instance in treating children; (2) there is continuous mixing of the blood inside the cellophane tube, which reduces the tendency towards a laminar flow, and thereby maintains a higher clearance-rate; (3) faults in the blood circuit, particularly leaks in the cellophane tube, can be repaired during a dialysis; and (4) this type of machine has been used successfully for over ten years. This machine can also remove water from the patient, when required.

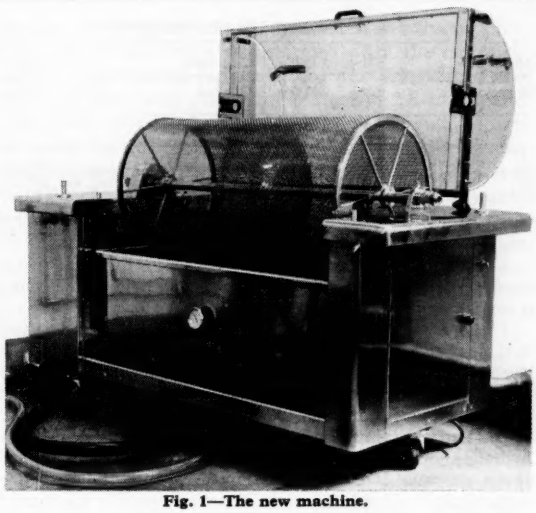

Fig. 1—The new machine.

Usifroid of Paris undertook to redesign the Necker Hospital modification of the Kolff-Brigham kidney (Hamburger and Richet 1956) to our specification (fig. 1).

*Description*

The main modifications to the original Necker Hospital model concerned the drum and the tank. The drum was lengthened to accommodate up to 195 ft. of cellophane tubing (24/32 in. inflated diameter), giving a maximum dialysing surface of about 3·2 sq. m. The tank had to be altered to accommodate this larger drum, the capacity being increased from 100 to 140 litres. This had the fortuitous advantage of maintaining a greater concentration gradient across the cellophane membrane throughout dialysis, and thereby slightly increasing the clearance-rate. Two pipes, each fitted with stopcocks, were fixed to the bottom of the tank for filling or emptying the irrigation fluid. Anti-splash plates were fitted to each pipe so that the tank could be filled from a thermostatically controlled mixing tap connected to the domestic hot and cold water, thus dispensing with the need for a separate storage tank.

So that one operator could supervise the machine more easily the direction of blood-flow through it was reversed, thereby allowing all the controls of the inflow and outflow blood-pumps and electrical circuits to be placed at one end of the machine. In practice many workers use an arteriovenous circuit which makes the inflow blood-pump unnecessary. If desired the outflow blood-pump can be placed at the end of the machine opposite to the controls.

The ' Perspex ' hood over the drum was redesigned so as to dip beneath the fluid level in the tank, as in the original model a gas mixture of 10% $CO_2$ and 90% $O_2$ introduced beneath the hood did not lower the pH of the fluid enough to prevent the precipitation of calcium. In the new model that we tested a flow-rate of 12 litres per minute of the gas mixture reduced the pH level of the tank fluid to that of normal blood (7·4 at 37°C) in about 25 minutes. This pH was maintained by reducing the flow-rate of the gas mixture to 2 litres per minute. These times should be checked for each machine.

This new model uses the same components as its predecessor. These have been designed with great care to prevent trauma to the blood; indeed the degree of hæmolysis is negligible. The polyvinyl-chloride tubing, rotary couplings, pumps, and venous reservoirs are sterilised by autoclaving, but the flow-meters must be sterilised chemically. The cellophane tubing should be soaked in water for at least twenty-four hours and then sterilised in boiling water for half an hour, the process being repeated three times. 2 pints (1080 ml.) of citrated

TABLE II—COMPOSITION OF BATH FLUID

| | | | |
|---|---|---|---|
| NaCl | 880 g. | Ca acetate | 26·6 g. |
| $NaHCO_3$ | 300 g. | Mg. acetate $4H_2O$ | 13·6 g. |
| K acetate | 45·5 g. | Glucose | 532 g. |

Leeds tap water 133 litres.

| | | | |
|---|---|---|---|
| Na | 140 mEq. per l. | Mg | 1·7 mg. per 100 ml. |
| K | 3·6 mEq. per l. | Ca | 6·0 mg. per 100 ml. |
| $HCO_3$ | 27·0 mEq. per l. | Cl | 113 mEq. per l. |

The upper half gives the weight of chemicals added to 133 litres of tap water, the lower half gives the ionic concentration.

blood are required to prime the apparatus before connecting it to the patient.

The composition of the fluid we used in the tank is given in table II. The final ionic strength of this fluid depends on the composition of the tap water, and in some areas the quantity of added chemicals may require adjustment. We adjust the concentration of sodium in the tank to equal the sodium-level of the patient's plasma when this has been lowered by over-hydration, otherwise the total body-sodium would be increased above normal. If the sodium increases during dialysis the extracellular fluid volume might expand as water is transferred from the intracellular fluid, and pulmonary œdema may follow. The sodium concentration in the tank can be adjusted to equal that in the plasma by adding either 880 or 800 g. of NaCl to the tank and water to the 133 or 140 litre marks that are engraved on the wall of the tank. When 880 g. of NaCl is used, with the other chemicals, 133 litres of water gives a final sodium concentration of 140 mEq. per litre, whilst 140 litres of water decreases the concentration to 133 mEq. per litre. The final concentrations of sodium using 800 g. of NaCl are 130 and 123 mEq. per litre respectively. This range of 123–140 mEq. per litre covers the concentration of sodium in plasma commonly met in patients with renal failure. The dilution of the other chemicals after increasing the volume of water in the tank to 140 litres is insignificant.

Recently a concentration of 1200 mg. per 100 ml. of glucose in the tank fluid has been advocated to counteract the osmotic pressure of plasma-proteins (Shackman 1959). In our experience this is unnecessarily high, for water has not been transferred into the patient with the larger machine, provided the sodium concentration is adjusted correctly.

*Clearance Studies*

Pure solutions were used to study the rate of clearance of urea and phosphate using the maximum dialysing surface of 3·2 sq. m., and a flow-rate of 500 ml. per minute. We compared these results with those from our own Kolff-Brigham dialyser, reducing its dialysing surface to 2·0 sq. m. and the flow-rate to 300 ml. per minute, to simulate the original Necker Hospital machine. This comparison is justified as the clearance-rates per unit length of cellophane were identical for the two machines.

To represent a patient a reservoir, containing 40 litres of fluid of the same composition as that used in the tank (table II) with the addition of 200 mg. per 100 ml. of urea (expressed as $N_2$) and 21 mg. per 100 ml. of phosphate (expressed as phosphorus), was connected to the machine. A stream of nitrogen was introduced at the bottom of the reservoir to ensure adequate mixing. During the six-hour dialysis the fluid in the tank was not changed two hourly, as is the usual practice during hæmodialysis. The fall in concentration of phosphate and urea $N_2$ in the fluid in the reservoir during the dialysis is shown in fig. 2 (*a* and *b*). The fall in phosphate level was far greater when using the new machine; hence the total quantity of phosphate removed during the dialysis was greater. As phosphate is dialysed relatively slowly (Wolf et al. 1951), and as the clearance-rate is not increased significantly at flow-rates greater than 300 ml. per minute (Parsons and McCracken 1958), the greater removal by the new machine is due mainly to the larger dialysing surface. During hæmodialysis the improved clearance will lower the phosphate level of the extracellular fluid more rapidly, and thus the diffusion gradient across the cell membrane will be increased, allowing the more rapid transfer of phosphate from the intracellular fluid. For urea (fig. 2*b*) the larger machine is also more effective. Indeed almost the maximum quantity of urea that could be removed from the fluid in the reservoir was extracted during the first three hours of dialysis, for then the urea level in the tank fluid had risen so much as to reduce significantly the diffusion gradient across the cellophane membrane. Had the fluid in the tank been changed every two hours, we calculated that the final B.U.N. level would have been 18 mg. per 100 ml., compared with 43 mg. for the original Necker machine of 2·0 sq. m. dialysing surface. The figures for phosphate would have been 7·3 and 11·0 mg. per 100 ml. respectively.

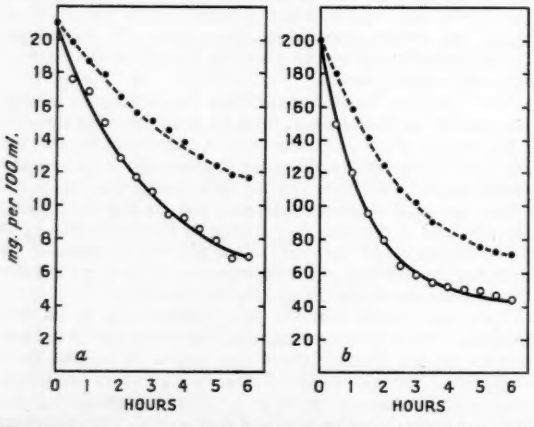


**Fig. 2—Comparison of the falls in (*a*) phosphorous level and (*b*) blood-urea-nitrogen, using the original (dotted lines) and the new (continuous lines) machines, during dialysis of 40 litres of pure solution.**

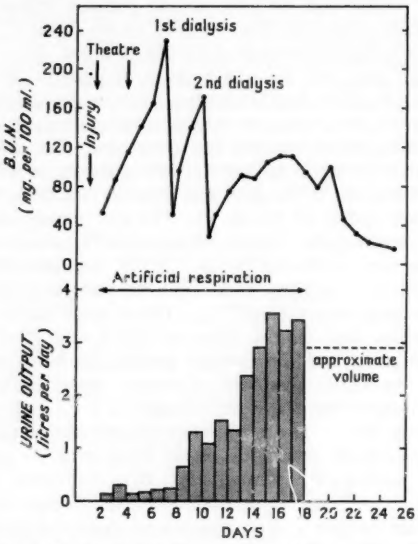


**Fig. 3—Some biochemical findings in a case of traumatic acute renal failure.**

*Technique for Removing Fluid*

It is not generally appreciated that the Kolff rotating-type of kidney can be used to remove water. To do this the concentration of glucose in the rinsing fluid should be increased to 1000 mg. per 100 ml. to increase the osmotic-pressure gradient across the cellophane membrane. The tendency to hyperglycæmia must be prevented by giving sufficient insulin to maintain the corporeal blood-sugar level at about 200 mg. per

100 ml. This procedure will cause the patient to lose 300 ml. of water every two hours. Higher concentrations of glucose in the rinsing fluid may increase the water loss without untoward reaction, for Boen (1959) has used a concentration of 4000 mg. per 100 ml. during peritoneal dialysis.

### Illustrative Case-report

The new machine was used to treat four patients in Leeds before it was installed in the department of urology of the Glasgow Royal Infirmary. All four Leeds hæmodialyses were uneventful, but as none of these patients had a high rate of protein breakdown the full value of the machine was not ascertained. The following case of traumatic anuria was treated with the new artificial kidney in Glasgow:

A previously healthy man of 36 (estimated weight 67 kg.) was admitted to the Glasgow Royal Infirmary on Jan. 1, 1960, after a motor-car accident. He was unconscious, with a deep frontal laceration, and extensive surgical emphysema over the right side of the chest and neck. He was cyanosed and respiration was laboured. X-ray examination revealed fractures of the left and right second ribs, and a right-sided pneumothorax. Two days after admission, at thoracotomy, the right lung was found to be completely avulsed from the trachea, though the pulmonary blood-vessels were intact. The bronchus was resutured to the trachea and the lung was inflated fully without evidence of leak at the site of reconstruction. Spontaneous respiration was not established for eighteen days, during which time adequate oxygenation was maintained by intermittent positive-pressure respiration utilising the tracheostomy that had been performed soon after admission.

Severe acute oliguric renal failure became apparent shortly after admission, and the B.U.N. rose steeply, reaching 228 mg. per 100 ml. on the seventh day, despite the usual conservative measures to suppress protein catabolism (fig. 3). A six-hour hæmodialysis resulted in a fall of B.U.N. to 49 mg. per 100 ml. and correction of the moderate acidosis and hyperkalæmia. (Cation-exchange resins had been used previously to control the hyperkalæmia.) The volume of urine increased the day after this dialysis, and the output quickly rose to higher than normal levels. But the B.U.N. continued to rise steeply, indicating an intense catabolic response, and on the tenth day a second hæmodialysis was performed. Within six hours the B.U.N. fell from 172 to 28 mg. per 100 ml. In neither dialysis was the intermittent positive-pressure respiration discontinued. After the second dialysis the B.U.N. again rose (despite a urinary volume of 3–4 litres per day and a urea excretion exceeding 30 g. per day) and then it remained around 93 mg. per 100 ml. for a week before a progressive fall.

The patient subsequently regained good renal function as judged by normal blood-chemistry, normal urine-urea concentration, and normal glomerular-filtration rate.

### Discussion

The mortality in patients with acute reversible renal failure is mainly dependent on the precipitating cause (Teschan et al. 1955, Bluemle et al. 1959, Parsons and McCracken 1959, Kiley et al. 1960, Loughridge et al. 1960). The results of treating patients with lesions from obstetric or medical causes are usually excellent. For example, in the obstetric group we anticipate a 90% recovery because complications are few, and the use of norethandrolone reduces protein breakdown (Blagg and Parsons 1960). On the other hand, surgical cases have proved unsatisfactory, mainly because of serious complications during renal failure.

During the first year we used our artificial kidney, the mortality-rate in surgical cases with rapid protein catabolism exceeded 75%. The commonest cause of death was sepsis; and, as a fair proportion of this seemed to arise from cross-infection in an open ward, the later patients were barrier-nursed in cubicles, and the prophylactic use of antibiotics was stopped. But the mortality was not significantly reduced. We next introduced our larger machine with a dialysing surface of 2·8 sq. m. and a maximum blood flow-rate of 500 ml. per minute, so that we could control the uræmia more adequately (Parsons and McCracken 1958). Although the incidence of overt staphylococcal infection became less, the mortality-rate in the surgical cases was not lowered. In accordance with the biochemical aspects outlined earlier, we decided that more balanced correction of the patients' biochemical abnormalities would be achieved by dialysing when the B.U.N. had reached 120–150 mg. per 100 ml. The mortality-rate in two comparable series with surgically induced acute reversible renal failure fell from 88 to 25% when earlier dialysis was instituted.

Even though the two series are small, we have no doubt that the new indication for dialysis in patients with rapid protein catabolism represents a considerable advance in clinical management. The most noticeable improvement was in the patients' resilience. Cerebration, unless disturbed by factors other than renal insufficiency, remained excellent throughout, and this contributed largely to the successful outcome. We also noted, for the first time in this group, spontaneous resolution of infection. This may have been the most important factor in the improved outcome. Study of the individual results (table I) shows that many patients in the earlier series died of sepsis late in their course (more than twelve days after the onset). This uncontrolled sepsis itself increases the severity of the protein breakdown, and postpones the recovery from renal failure. Our results suggest that earlier dialysis breaks this vicious circle. To this end, patients should be transferred to an artificial-kidney unit as soon as it is realised that they have acute renal failure due to trauma, or have a rapidly rising B.U.N. (over 30 mg. per 100 ml. per day).

The improvement gained by earlier dialysis does not necessarily signify that the clinical course is benign. On the contrary, the longer the survival the more frequent are other complications, which usually arise from the original surgical procedure, or from the cardiovascular system if this was not previously healthy. It was in the management of the surgical complications that the larger machine proved invaluable, for it usually gave us thirty-six to forty-eight clear hours between dialyses to attend to the patient's other needs. We found that mobility and chest exercises were very necessary; and some patients needed investigatory procedures and further surgical operations. When a less efficient machine is used with the same principles of management (Teschan et al. 1959, Scribner et al. 1960b, Scribner and Caner 1960), the frequency of dialysis must be a serious limitation to performing these procedures. In addition, we consider that the machine should be capable of correcting the biochemical abnormalities in patients with very rapid protein catabolism (say a B.U.N. rising by 80 mg. per 100 ml. per day). At first we found that a machine with a dialysing surface of 2·0 sq. m. was incapable of dealing with these cases, whereas our modified model handled them fairly satisfactorily.

The new machine has a dialysing surface of 3·2 sq. m. The larger area was chosen so as to improve still further the clearance-rate of the more slowly diffusible substances. The good clinical and biochemical results in the severe traumatic case treated by this new machine in Glasgow are encouraging.

When assessing the improvement from earlier dialysis of patients with rapid protein catabolism, more balanced correction of the uræmic state is not the only contributing factor; we have also limited the accumulation of those substances that are dialysed relatively quickly. Although the latter may prove equally important, we have seen good results in patients who, for various reasons, have been dialysed for eight hours when the B.U.N. had reached 180–200 mg. per 100 ml. But many patients do not tolerate this technique well, and we have therefore not treated a comparable series.

*Indications for Dialysis using a Surface of 2·8 or 3·2 sq. m.*

In patients with a mild or moderate rate of protein catabolism (B.U.N. rising less than 30 mg. per 100 ml. per day) the recovery-rate exceeded 90% even though dialysis was performed when uræmia was causing early clinical deterioration (Parsons and McCracken 1959). We have not varied this policy during the past eighteen months, and the recovery-rate has remained the same. We therefore do not advise earlier dialysis except perhaps for elderly patients, or those with preexisting cardiovascular disease, or if severe infection may arise. The good results in these two groups are probably due firstly to the infrequent complications (only a minority underwent trauma), and secondly to our larger machine, for most of these patients regain renal function before a second dialysis becomes necessary.

In patients with severe renal failure (B.U.N. rising more than 30 mg. per 100 ml. per day) we advocate dialysis as soon as the B.U.N. reaches 120–150 mg. per 100 ml. If the B.U.N. has inadvertently been allowed to reach 180–200 mg. dialysis lasting eight hours will produce more balanced correction of the abnormalities; but if this longer dialysis is unlikely to be tolerated, it should be discontinued and further dialysis performed some twenty-four to forty-eight hours later. If a smaller machine is used then dialysis should be performed continuously (Scribner and Caner, 1960), or daily (Teschan et al. 1959), or on alternate days (Scribner et al. 1960b).

As the clearance-rates achieved with this new machine are very much higher than with most other types, we advise altering the timetable for dialysis in certain special situations. The majority of patients in very advanced acute uræmia with severe clinical manifestations (such as pronounced hypotension, convulsions, or coma), or in advanced chronic uræmia, seem to have adapted to the abnormal biochemical state, and they respond adversely when their uræmia is corrected too rapidly. We have found that four hours' dialysis should be performed at first; this has about the same effect as a six-hour dialysis with a machine of 2·0 sq. m. dialysing surface. Further correction of the uræmic state in acute cases should be delayed for some twelve to twenty-four hours; untoward delay is often unwise because many of these patients have an increased rate of protein breakdown, resulting from advanced uræmia, which cannot be controlled until the biochemical abnormalities are corrected. In chronic cases a suitable period between the first and second dialyses would be three to four days. For children the dialysing surface should be reduced to 1·5 or 2·0 sq. m.

This new machine (with the dialysing surface increased to 3·2 sq. m.) represents, we believe, considerable advance in the management of all patients with acute reversible renal failure. In particular it has been designed to correct adequately the biochemical abnormalities in patients with rapid protein breakdown. With its use, when dialysis is performed at the appropriate time, the mortality-rate should be reduced to more reasonable proportions.

**Summary**

In hæmodialysis the use of a larger dialysing surface seems to give more balanced correction of the uræmic state. In patients with acute renal failure and a high rate of protein catabolism, dialysis is indicated when the blood-urea-nitrogen reaches 120–150 mg. per 100 ml. The mortality-rate in a group of " surgical " patients so treated was very much lower than in a similar group in whom dialysis was delayed until the onset of clinical deterioration.

A new artificial kidney is described with a dialysing surface of 3·2 sq. m., and other modifications. In patients with rapid protein catabolism adequate correction of the uræmia can be achieved by dialysing with this new machine as the blood-urea nitrogen reaches 120–150 mg. per 100 ml.

We are indebted to Dr. O. Ciniewicz, Dr. D. R. Bell, Mr. D. W. Daly, Mr. J. M. Gray, Mr. W. M. L. Laubscher, Mr. I. M. Lister, Mr. F. G. Smiddy, and Mr. Irving Smith for assistance with the clinical management of the patients; to Sister M. Thwaites, Sister M. Sharpe, and Sister F. N. Ellis for their nursing care; to Mr. B. Auty for technical assistance during the hæmodialyses; and to Dr. William Goldie for many helpful suggestions. The new artificial kidney was manufactured by Usifroid S.A., 9, rue Moreau-Vauthier, Boulogne/Billancourt (Seine), France; the London agents are Bourbon Products Ltd., 12, Park Place, London, S.W.1.

Part of the cost of this research was provided by the board of governors of the United Leeds Hospitals.

The new artificial kidney has been used for over a year in the Royal Infirmary, Glasgow. We thank Dr. A. C. Kennedy for helpful suggestions in the preparation of this paper, and, with Mr. John Thomson and Dr. William Jones for providing the report of the case treated in Glasgow.

REFERENCES

Blagg, C. R., Parsons, F. M. (1960) *Lancet*, ii, 577.
Bluemle, L. W., Jr., Webster, G. D., Elkinton, J. R. (1959) *Arch. intern. Med.* **104**, 180.
Boen, S. T. (1959) Peritoneal Dialysis. Netherlands.
Hamburger, J., Richet, G. (1956) *Rev. franç. Étud. clin. biol.* **1**, 39.
Kiley, J. E., Powers, S. R., Beebe, R. T. (1960) *New Engl. J. Med.* **262**, 481.
Loughridge, L. W., Milne, M. D., Shackman, R., Wootton, I. D. P. (1960) *Lancet*, i, 351.
Merrill, J. P., Thorn, G. W., Walter, C. W., Callahan, E. J., III, Smith, L. H. (1950) *J. clin. Invest.* **29**, 412.
Murphy, W. P., Jr., Swan, R. C., Walter, C. W., Weller, J. M., Merrill, J. P. (1952) *J. Lab. clin. Med.* **40**, 436.
Parsons, F. M. (1959) *Irish J. med. Sci.* p. 184.
— (1960) Modern Trends in Urology; p. 40. London.
— McCracken, B. H. (1958) *Brit. J. Urol.* **30**, 463.
— — (1959) *Brit. med. J.* i, 740.
Scribner, B. H., Caner, J. E. Z. (1960) *Clin. Res. Proc.* **8**, 136.
— — Buri, R., Quinton, W. (1960a) *Trans. Amer. Soc. artif. intern. Organs* (in the press).
— Magid, G. J., Burnell, J. M. (1960b) *Clin. Res. Proc.* **8**, 136.
Shackman, R. (1959) Recent Advances in Surgery; p. 166. London.
Teschan, P. E., O'Brien, T. F., Baxter, C. R. (1959) *Clin. Res. Proc.* **7**, 280.
— Post, R. S., Smith, L. H., Jr., Abernathy, R. S., Davis, J. H., Gray, D. M., Howard, J. M., Johnson, K. E., Klopp, E., Mundy, R. L., O'Meara, M. P., Rush, B. F., Jr. (1955) *Amer. J. Med.* **18**, 172.
Wolf, A. V., Remp, D. G., Kiley, J. E., Currie, G. D. (1951) *J. clin. Invest.* **30**, 1062.

# ALLYLESTRENOL : A NEW ORAL PROGESTOGEN

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IN the past few years several orally active synthetic progestogens have become available. These have been derivatives of 19-norandrostenolone and appear to occupy a position chemically between the natural androgens and œstrogens. Although several of these substances have displayed, both in laboratory animals and in the human, remarkably potent progestogenic effects, various undesir-

able side-effects have been described. Of these, perhaps the two most important have been symptoms of intolerance and a tendency to virilisation; and in several cases protracted administration for pregnancy maintenance has resulted in pseudohermaphroditism in the offspring.

One of the newer members of the group—allylestrenol (' Gestanin ', Organon)—although pharmacologically less active as a progestogen than some members of the group, seems to be completely free from androgenic activity and is exceptionally well tolerated. We have tested this preparation in over 50 cases of various pathological states, and give here a preliminary account of the results of such treatment over periods varying from three to six months.

## Material

The cases treated fall into four main groups:

1. *Premenstrual tension:* 13 cases (1 associated with premenstrual spotting).
2. *Abortion:* 14 cases (threatened abortion and probable failure of nidation).
3. *Menstrual disturbances:* 18 cases (menorrhagia, amenorrhœa, anovular menstruation, and true metropathia).
4. *Dysmenorrhœa:* 4 cases (primary dysmenorrhœa, probable endometriosis with premenstrual and menstrual pain.

## Results

### *Premenstrual Tension*

Most of the 13 patients in this group had the typical multiplicity of symptoms including depression, insomnia, weight increase, and irritability; several had severe breast discomfort and premenstrual diarrhœa or constipation. 1 at the age of 32 displayed premenstrual spotting and staining for several days before the onset of the true menstrual flow; this had not responded to repeated curettage and the application of two cauteries to the cervix for slight erosion. This is the only case in which a biopsy specimen of the endometrium is available, and it showed a highly secretory phase with no evidence of progestogenic deficiency.

The 13 patients were treated with 5–10 mg. allylestrenol daily for three to five days in each menstrual cycle, usually starting three days before the expected onset of symptoms and ending three days before the period was due.

8 were greatly improved; 2 were improved but with much increase in libido; 1 was moderately improved; 2 were unimproved, and during treatment complained of severe low pelvic pain.

### *Abortion Syndrome, Threatened Abortion, Failure of Nidation*

In all 6 cases of *recurrent abortion* the patients had had three abortions in eighteen months, each taking place between the sixth and tenth weeks of gestation. In each of these cases previous biopsy had shown poor secretory activity two to five days before the onset of menstruation.

These 6 cases were treated with 15 mg. allylestrenol daily from the sixteenth to the twenty-sixth day of the cycle for three months.

1 conceived in the first cycle, 3 in the second, and 1 in the third. 1 showed full secretory endometrium but failed to conceive.

The 5 who became pregnant were given a further course of treatment consisting of 10 mg. daily for sixteen weeks. 3 maintained their pregnancy to term, 1 had another abortion at the twelfth week, and 1 went to term despite several small hæmorrhages during the earlier weeks of treatment.

1 case of *threatened abortion* was treated. The patient, who had previously had one normal pregnancy to term, received 15 mg. of allylestrenol daily from the tenth week of pregnancy to a total of 150 mg. and was rested in bed. Bleeding continued and eventually required curettage: the conceptus was probably already blighted. There was no evidence of intolerance to the drug.

7 cases were treated in which recurrent *failure of nidation* was suspected. The endometrium had shown poor secretory activity, the temperature chart gave a low biphasic reading, but regular ovulation seemed probable. Seminal-fluid investigation had shown no abnormalities. Patients in this series had a normal cycle generally, but every two or three months the period would be extended by anything up to sixteen days, the onset being slow and associated with backache, and the flow being dark brown and scanty before establishing itself. The loss was not always excessive; frequency and constipation were common symptoms, but breast activity was not usual. Patients were advised to avoid pregnancy for two months.

These 7 patients were given 15 mg. of allylestrenol daily from the sixteenth to the twenty-sixth day of each cycle for two months.

Biopsy specimens in the immediate premenstrual phase showed secretory activity.

5 patients became pregnant within the three or four months after biopsy. 1 of them aborted at the eighth week.

2 did not conceive, though treatment was continued for a total of eight months.

### *Menstrual Disturbances*

2 cases of *secondary amenorrhœa* were treated. Both had previously had one child.

These patients received 10 mg. allylestrenol daily for twenty days in two successive cycles. No œstrogen priming was given.

Neither patient had any menstrual loss.

6 cases of *menorrhagia* were treated, all being selected to preclude the possibility of bleeding from any cause other than hormonal imbalance. All patients had been treated with hormones or by curettage over the previous eighteen months with temporary or little relief. Testosterone had been valuable in 2 out of 3, but had been discontinued because of unpleasant side-effects.

5 of these patients were given 15 mg. of allylestrenol daily from day 12 to day 26. In 3 the results were satisfactory, and the period of bleeding was reduced from between nine and twelve days to between five and seven days. The loss remained heavy but was controllable and became less with each successive cycle. The onset and finish of bleeding were clear-cut. 2 failed to respond adequately, and after two cycles treatment was stopped.

The 6th patient, who received 15 mg. of allylestrenol from the fifth to the twenty-fifth day, had such severe hæmorrhage that hysterectomy was performed after one cycle.

4 cases of *metropathia* were treated. All had a history of complete irregularity of bleeding over periods of seven months to two and a half years. 2 cases showed anæmia with hæmoglobin under 70%. All had had curettage and no abnormal pelvic pathological changes were reported. Endometrial biopsy in each case showed the typical pattern of irregular epithelial shedding. Before treatment

was started a medical curettage was attempted in all patients, using 'Menstrogen' tablets. The resulting bleeding was taken to represent the first day of a new cycle, and treatment during the latter half of this cycle produced regular periods and normal loss for the patient.

These patients were all given 15 mg. allylestrenol daily from day 12 to day 26 for four cycles.

3 of them showed secretory endometrium after three months. Similar appearances were seen in biopsy material taken two months later.

2 showed some improvement, but the biopsy specimens were described as "poor secretory in character". After treatment was stopped, loss again became irregular and variable in amount.

1 patient became pregnant.

6 other patients, in whom the menstrual losses were clearly *anovular*, were primed with œstrogens (ethinyl œstradiol 0·05 mg. twice daily) from day 7 to day 21. They were then treated with allylestrenol 10 mg. daily from day 19 to day 24.

In all of them full secretory endometrium and satisfactory luteal phases were produced in a shorter time than with any other luteinising substances.

*Dysmenorrhœa*

Endometriosis was diagnosed in 2 out of 6 patients with *dysmenorrhœa*. 1 of them, in whom the diagnosis was confirmed by laparotomy, received 10 mg. of allylestrenol daily from day 14 to day 24 for three months. The other was given 1200 mg. of allylestrenol over a period of five months, the dose being steadily increased.

The patient with confirmed endometriosis had less pain after treatment, but the result must be considered unsatisfactory. The other had break-through bleeding twice, but there was no pain during treatment or for the three cycles afterwards.

4 patients with typical *primary dysmenorrhœa* were treated. 2 of them received 10 mg. of allylestrenol daily from day 5 to day 25 for three months, with excellent results. The others were given 10 mg. daily from day 6 to day 22 with some slight improvement; but treatment had to be stopped because of increased libido.

### Discussion

The search for a satisfactory oral substitute for progesterone has been carried further by this preliminary trial of allylestrenol. Clearly, this substance is not the most potent of the synthetic orally active progestogens now available, but this is unimportant. Allylestronol seems to have the advantage of being extremely well tolerated, and to have given the results that could have been expected of a progestogen. The effect upon dysmenorrhœa is perhaps a little surprising since progesterone usually increases the discomfort. The apparent increase in libido induced in 2 cases is also surprising since the pharmacological examination of allylestrenol shows it to be not androgenic. These unusual features will need further study.

### Summary

A new synthetic orally active progestogen, allylestrenol ('Gestanin'), has been used in general gynæcological practice in more than 50 cases and has proved in most cases a satisfactory oral progestogen.

We thank Dr. Raymond Greene, director of the parenthood clinic, Royal Northern Hospital, London, for permission to report 3 of the present cases. The allylestrenol was kindly supplied by Organon Laboratories Ltd.

## PROTEINS OF SERUM AND ŒDEMA FLUID IN ANOXIC COR PULMONALE

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BOTH in animals and man, anoxia causes an increase in the permeability of capillaries to protein (Landis 1928, Maurer 1940, 1941, Henry et al. 1947, Hendley and Schiller 1954). This increase in permeability has been suggested as a possible causative factor in œdema in patients with heart-failure (Smirk 1936, Landis 1946). If this hypothesis is correct, one would expect that the protein level of the œdema fluid of patients with pulmonary heart-failure in whom the arterial oxygen saturation is reduced (Baldwin et al. 1949, Platts 1953), would show evidence of a high capillary permeability to protein. This communication reports a study by paper-electrophoresis of the proteins of serum and œdema fluid of such patients.

### Material and Methods

Eleven patients with heart-failure secondary to chronic bronchitis and emphysema were studied (table I).

Venous blood-samples were obtained without stasis. 25 ml. of œdema fluid was collected by Southey's tubes inserted in the legs, care being taken to obtain blood-free specimens of fluid.

Total nitrogen concentration was determined in serum and œdema fluid by the macrokjeldahl method. Non-protein-nitrogen concentration was determined on the filtrate from 5 ml. of œdema fluid after precipitation in 25% trichloracetic acid. Total protein content was calculated using a factor of 6·25. Œdema fluid was concentrated against a 12% w/v dextran solution, and then paper-electrophoretic analysis of serum and concentrated œdema fluid was carried out by the method of Flynn and de Mayo (1951). The strips were stained with bromphenol blue and scanned with a photoelectric densitometer; the areas under the resulting curves were measured with a planimeter.

### Results

The results are recorded in tables I and II, and in figs. 1 and 2.

The total serum-protein level was below normal in five of the eleven patients, in all but one of whom the albumin level was lower than the total globulin level. In all the patients, the total protein content of the œdema fluid was much lower than that of the serum, and there was no relation between the protein contents of the two fluids (fig. 1). There was, however, a direct relation between the relative levels of the different protein fractions of the serum and œdema fluid (fig. 2). The percentage of albumin—and, hence, the ratio of albumin to globulin—was always greater in the œdema fluid than in the serum. The percentage of $\alpha_1$-globulin in the œdema fluid was almost always greater than that in the serum, whereas the reverse was usually true of the percentages of the other three globulin fractions. The greatest difference in the globulin fractions of the two fluids was the consistently lower percentages of $\alpha_2$-globulin in the œdema fluid (table II and fig. 2).

### Discussion

A reduction in the levels of both total protein and albumin resembling that found in the serum of several of the present patients has been described in subjects with heart-failure from other causes (Ellis 1933, Hand 1934, Thomson 1934, Hammond and Ross 1960). The total protein levels of the œdema fluids of the present patients

TABLE I—TOTAL PROTEIN, ALBUMIN, AND TOTAL GLOBULIN CONCENTRATIONS OF PAIRED SPECIMENS OF SERUM AND ŒDEMA FLUID

| Patient | Age | Sex | Chest disease | Arterial oxygen saturation (%) | Arterial $pCO_2$ (mm.Hg) | Serum | | | | | Œdema fluid | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | (mg. per ml.) | Albumin (%) | Albumin (mg. per ml.) | Total globulin (%) | Total globulin (mg. per ml.) | (mg. per ml.) | Albumin (%) | Albumin (mg. per ml.) | Total globulin (%) | Total globulin (mg. per ml.) |
| A | 61 | F | Chronic bronchitis and emphysema | 64 | 52 | 61·5 | 40·2 | 24·7 | 59·8 | 36·8 | 2·58 | 49·2 | 1·27 | 50·8 | 1·31 |
| B | 40 | M | | 63 | 62 | 47·0 | 47·3 | 22·2 | 52·7 | 24·8 | 1·50 | 52·1 | 0·78 | 47·9 | 0·72 |
| C | 62 | M | | .. | .. | 67·0 | 43·0 | 28·8 | 57·0 | 38·2 | 4·38 | 49·1 | 2·15 | 50·9 | 2·23 |
| D | 62 | M | | .. | .. | 56·4 | 39·8 | 22·5 | 60·2 | 33·9 | 1·25 | 48·4 | 0·61 | 51·6 | 0·64 |
| E | 60 | M | | 60 | 58 | 65·6 | 42·3 | 27·7 | 57·7 | 37·9 | 1·85 | 46·6 | 0·86 | 53·4 | 0·99 |
| F | 58 | M | | 65 | 92 | 57·1 | 40·4 | 23·0 | 59·6 | 34·1 | 2·62 | 51·0 | 1·34 | 49·0 | 1·28 |
| G | 64 | M | | 59 | 67 | 58·7 | 53·2 | 31·2 | 46·8 | 27·5 | 0·94 | 64·3 | 0·61 | 35·7 | 0·33 |
| H | 46 | M | | 70 | 81 | 61·0 | 46·2 | 28·1 | 53·8 | 32·9 | 6·40 | 54·4 | 3·48 | 45·6 | 2·92 |
| J | 58 | M | | .. | .. | 53·5 | 42·1 | 22·5 | 57·9 | 31·0 | 1·62 | 50·0 | 0·81 | 50·0 | 0·81 |
| K | 52 | M | | 69 | 60 | 60·6 | 45·8 | 27·7 | 54·2 | 32·9 | 2·38 | 55·3 | 1·32 | 44·7 | 1·06 |
| L | 52 | M | | 68 | 51 | 66·5 | 40·6 | 27·0 | 59·4 | 39·5 | 3·30 | 51·8 | 1·71 | 48·2 | 1·59 |
| Mean | 56 | | | 65 | 65 | 59·5 | 43·7 | 26·0 | 56·3 | 33·5 | 2·62 | 52·0 | 1·36 | 48·0 | 1·26 |

are also similar to those found in the œdema fluid of other types of heart-failure (Bramkamp 1935, Crockett 1956, Hammond and Ross 1960). The only previously reported protein levels in œdema fluid in patients with heart-failure secondary to emphysema are those given by Stead and Warren (1944), who studied two such patients. Stead and Warren thought that the low total protein levels in the œdema fluid of these patients, who were definitely anoxic, showed that increased capillary permeability to protein was of no importance in the pathogenesis of the œdema. As Hammond and Ross (1960) have pointed out, the total protein content of œdema fluid depends not only on the protein content of the capillary filtrate but also on the relative rates of reabsorption into the circulation of fluid and protein from this filtrate. Exton-Smith and Crockett (1958) showed that the relative levels of albumin and the various globulin fractions of œdema fluid are of value in assessing the degree of capillary permeability to protein. In œdema associated with conditions in which capillary permeability is believed to be normal, Exton-Smith and Crockett found that the percentage of $\alpha_2$-globulin was always much lower in the œdema fluid than that in the serum. In the patients who were suffering from considerable anoxia (table I), the percentage of $\alpha_2$-globulin was always less in the œdema fluid than in the serum. In fig. 2, the slope of the line relating the percentages of $\alpha_2$-globulin in serum and in œdema fluid is clearly the least steep. This indicates that there is a greater reduction in the percentage of this fraction in the œdema fluid compared with the serum than in that of any of the other proteins present in these fluids. Hence, a reasonable conclusion is that the œdema fluid of patients with anoxic cor pulmonale is associated with capillaries of normal permeability, and that an increase in capillary permeability to protein is not a factor in its formation. The present results, therefore, support the hypothesis that any changes in the permeability to protein of the capillaries of patients with heart-failure are very small and of little importance in the pathogenesis of œdema (Hammond 1959).

TABLE II—PERCENTAGES OF THE GLOBULIN FRACTIONS OF PAIRED SPECIMENS OF SERUM AND ŒDEMA FLUID

| Patient | Serum globulins (%) | | | | Œdema globulins (%) | | | |
|---|---|---|---|---|---|---|---|---|
| | $\alpha_1$ | $\alpha_2$ | $\beta$ | $\gamma$ | $\alpha_1$ | $\alpha_2$ | $\beta$ | $\gamma$ |
| A | 5·4 | 13·9 | 17·9 | 22·6 | 8·9 | 9·9 | 17·4 | 14·6 |
| B | 5·0 | 9·3 | 16·9 | 21·5 | 6·8 | 7·2 | 16·8 | 17·1 |
| C | 7·2 | 13·3 | 20·2 | 16·3 | 8·2 | 8·3 | 17·3 | 17·1 |
| D | 5·8 | 16·1 | 14·7 | 23·6 | 9·7 | 9·7 | 13·1 | 19·1 |
| E | 7·1 | 9·7 | 17·3 | 24·2 | 7·1 | 6·5 | 16·0 | 23·8 |
| F | 6·6 | 15·3 | 19·0 | 18·7 | 9·0 | 7·0 | 15·2 | 17·8 |
| G | 6·7 | 10·7 | 14·8 | 14·6 | 9·7 | 3·5 | 11·5 | 11·0 |
| H | 5·2 | 11·4 | 15·9 | 21·3 | 6·4 | 5·3 | 15·9 | 18·0 |
| J | 8·5 | 14·3 | 18·7 | 16·4 | 12·8 | 7·4 | 15·9 | 13·9 |
| K | 3·9 | 3·7 | 18·8 | 27·8 | 7·2 | 3·4 | 13·4 | 20·7 |
| L | 5·4 | 11·7 | 19·7 | 22·6 | 9·3 | 9·1 | 16·7 | 13·1 |
| Mean | 6·1 | 11·8 | 17·6 | 20·9 | 8·7 | 7·0 | 15·4 | 16·9 |

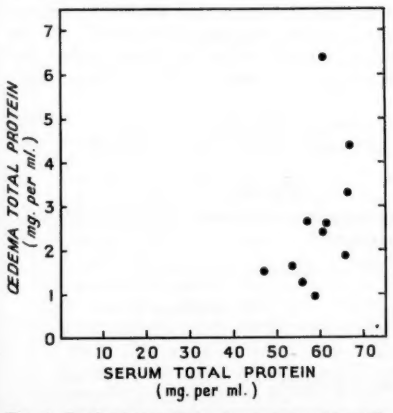


Fig. 1—Lack of correlation between total protein concentration of œdema fluid and serum.

## Summary

The total protein content has been measured in serum and œdema fluid from eleven patients with anoxic cor

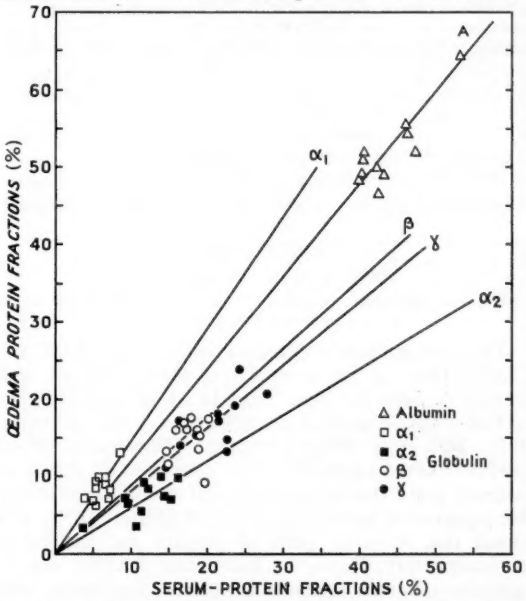


Fig. 2—Relation between percentages of albumin and four globulin fractions in œdema fluid and serums.

The regression lines have been drawn through the origin and the means for each fraction.

pulmonale. Paper-electrophoresis has been used to separate the proteins into albumin and globulins.

The total serum-protein content was often below normal, but was always very much greater than that of the œdema fluid.

The percentages, but not the levels, of the albumin and the various globulin fractions of the œdema fluid were directly related to the corresponding percentages of the serum. The percentage of $\alpha_2$-globulin in the œdema fluid was always much lower than that in the serum.

The conclusion may be drawn that an increase in capillary permeability to protein plays little or no part in the pathogenesis of cardiac œdema.

I should like to thank Prof. C. H. Stuart-Harris for permission to study patients admitted under his care, and Miss B. Ibbotson for excellent technical assistance.

REFERENCES

Baldwin, E. de F., Cournand, A., Richards, D. W. (1949) *Medicine, Baltimore*, **28**, 201.
Bramkamp, R. G. (1935) *J. clin. Invest.* **14**, 34.
Crockett, D. J. (1956) *Lancet*, ii, 1179.
Ellis, L. B. (1933) *Med. Clin. N. Amer.* **16**, 943.
Exton-Smith, A. N., Crockett, D. J. (1957) *Brit. med. J.* ii, 1280.
Flynn, F. V., de Mayo, P. (1951) *Lancet*, ii, 235.
Hammond, J. D. S. (1959) M.D. Thesis, University of Sheffield.
— Ross, R. S. (1960) *Clin. Sci* **19**, 119.
Hand, H. M. (1934) *Arch. intern. Med.* **54**, 215.
Hendley, E. D., Schiller, A. A. (1954) *Amer. J. Physiol.* **179**, 216.
Henry, J., Goodman, J., Meehan, J. (1947) *J. clin. Invest.* **26**, 1119.
Landis, E. M. (1928) *Amer. J. Physiol.* **83**, 528.
— (1946) *Ann. N.Y. Acad. Sci.* **46**, 713.
Maurer, F. W. (1940) *Amer. J. Physiol.* **131**, 331.
— (1941) *ibid.* **133**, 170.
Platts, M. M. (1953) *Clin. Sci.* **12**, 64.
Smirk, F. H. (1936) *ibid.* **2**, 317.
Stead, E. A., Warren, J. V. (1944) *J. clin. Invest.* **23**, 283.
Thomson, W. A. R. (1934) *Quart. J. Med.* **3**, 587.

# NIALAMIDE (NIAMID) IN ANGINA PECTORIS

## Report of a Double-blind Trial

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THE excellent results obtained by Cesarman (1957) and Cossio (1958) in the treatment of angina pectoris with iproniazid have not been reproduced in carefully controlled trials (Dewar et al. 1959, Snow and Anderson 1959, Fife et al. 1960). Although Towers and Wood (1958) reported significant improvement in 31 out of 41 patients given this drug, their trial was not controlled. No report is as favourable as that of Master (1958), who stated that in many years of practice and interest in coronary-artery disease he had found nothing else so effective. Other monoamine-oxidase inhibitors have recently been introduced to try to preserve the activity of iproniazid while diminishing the incidence of toxic effects. Mackinnon et al. (1960) reported considerable improvement in 11 of 27 patients given pheniprazine hydrochloride (N-α-methylphenethyl hydrazine hydrochloride, 'Cavodil'), during a double-blind trial, but Phear and Walker (1960) observed improvement in only 1 patient out of 20 receiving 1-benzyl-2-pivaloylhydrazine ('Tersavid').

This report describes a double-blind trial of a monoamine-oxidase inhibitor, nialamide (N-[2-benzylcarbamoylethyl]-$N^1$-isonicotinoylhydrazine, 'Niamid').

### Material and Methods

Only patients with typical angina pectoris caused by coronary-artery disease were admitted to the trial, and care was taken to exclude patients with aortic-valve disease, thyrotoxicosis, or myxœdema. Other grounds for exclusion were a positive blood Wassermann reaction, a hæmoglobin level of less than 11·0 g. per 100 ml. or an erythrocyte-sedimentation rate exceeding 20 mm. in the first hour (Wintrobe). Recent myocardial infarction was excluded as far as possible on clinical grounds and by electrocardiographic examination. No patient was included in the trial if the diagnosis was uncertain.

The trial was conducted simultaneously at five different hospitals, and each physician was responsible for his group of cases. Sufficient patients were collected quickly, so that the possible effect of different weather conditions was minimised. The trial was divided into four periods.

During the first two weeks patients were observed, but were given no additional treatment; and throughout the trial they continued any previous medication such as trinitrin, long-acting nitrites, or long-term anticoagulant therapy. During the second and fourth periods of four weeks, each patient received either nialamide (one 25 mg. tablet three times daily) or a control tablet identical in appearance. These tablets were dispensed on a double-blind basis, and the order in which they were given was determined by random selection. Because of the prolonged action of certain monoamine-oxidase inhibitors, these two four-week periods were interrupted by a third period of two weeks when each patient received an inert tablet, also identical in appearance to the other two. The physicians—but not the patients—were aware that an inert preparation was being dispensed during this stage.

Throughout the trial patients were asked to record the number of anginal attacks during each twenty-four hours, and were encouraged to keep their activities at a steady level. They were also asked to record any side-effects. Progress was assessed at weekly visits to their physician, and an additional check on the response was made by counting the number of trinitrin tablets used since the previous week. The blood-pressure and pulse-rate were recorded at each interview; and electrocardiographic examination, full blood-picture investigation and liver-function tests carried out during the initial two weeks, during the middle two weeks when an inert preparation was given, and at the end of the trial.

31 patients entered the trial; one man aged 54 died from myocardial infarction, and a woman aged 47 was withdrawn because acute subendocardial ischæmia developed. A 3rd patient had to be withdrawn owing to severe nausea and vomiting. All these 3 patients were in fact receiving control tablets.

Of the 28 patients who completed the trial, 17 were men and 11 women; their ages ranged from 29 to 76 years, the average being 58·5 years.

### Results

The 28 patients may be considered under four headings (see accompanying table).

RESULTS OF TREATMENT IN 28 CASES

| Result | No. of patients | % |
|---|---|---|
| *Improvement:* | | |
| With nialamide alone .. .. | 7 | 25 |
| With control alone .. .. | 1 | 3·6 |
| With both nialamide and control | 9 | 32·1 |
| No improvement .. .. .. | 11 | 39·3 |
| Total .. .. .. .. .. | 28 | 100 |

7 patients improved on nialamide alone; in 4 the improvement was both subjective and objective, judged by the decrease in number of attacks, as well as by trinitrin requirements. The remaining 3 felt better on nialamide, but the number of their attacks did not diminish greatly. Possibly these patients had a greater exercise-tolerance; alternatively, their pain was less sustained and severe; but the frequency of attacks remained the same. Or perhaps these patients simply experienced an enhanced sense of well-being on nialamide.

The difference between the improvement with nialamide (25%) and control tablets (3·6%) just fails to reach the 5% level of significance ($P=0·07$), and a larger series might have shown a significant difference in favour of nialamide. The 9 patients who improved on both nialamide and control tablets did so in a uniform manner throughout the trial, irrespective of the order in which they received the tablets. This suggests the so-called ski-slope response expected by Cole et al. (1957) in some anginal patients enjoying the extra care and attention inseparable from a therapeutic trial. If this group is included in the assessment it will be seen that 16 patients (57%) improved on nialamide, and 10 (36%) on control tablets. This difference is not statistically significant. No side-effects of nialamide were reported by any patient. No changes in the blood-picture or abnormalities in liver-function tests were observed, and nialamide caused no significant fall in blood-pressure.

### Conclusions

This trial suggests that nialamide in a dosage of 25 mg. t.d.s. benefits some patients with angina pectoris. Because the numbers are small our results are not statistically significant.

Nialamide, in common with other monoamine-oxidase inhibitors tested in double-blind trials, appears to lack the almost magical effect originally claimed for iproniazid in suppressing anginal pain.

This trial again demonstrated the need for adequate controls. If these 28 patients had been given nialamide without any controls, 16 (57%) would have apparently benefited.

We are indebted to Dr. P. Armitage for advice concerning the statistical aspects of the trial. The Niamid brand of nialamide tablets were kindly supplied by Dr. A. I. MacPhail, of Harvey Pharmaceuticals.

REFERENCES

Cesarman, T. (1957) *Arch. Inst. Cardiol. Mex.* **27**, 563.
Cole, S. L., Kaye, H., Griffith, G. C. (1957) *Circulation*, **15**, 405.
Cossio, P. (1958) *Amer. Heart J.* **56**, 113.
Dewar, H. A., Horler, A. R., Newell, D. V. (1959) *Brit. Heart J.* **21**, 315.
Fife, R., Howitt, G., Stevenson, J. (1960) *Brit. med. J.* i, 692.
Mackinnon, J., Anderson, D. E., Howitt, G. (1960) *ibid.* p. 243.
Master, A. M. (1958) *Amer. Heart J.* **56**, 570.
Phear, D., Walker, W. C. (1960) *Brit. med. J.* ii, 995.
Snow, P. J. D., Anderson, D. E. (1959) *Brit. Heart J.* **21**, 323.
Towers, M. K., Wood, P. (1958) *Brit. med. J.* ii, 1067.

" . . . Cuttlefish are animals that shamefully neglect their young. They lay eggs and then go away and forget about them. This poses something of a problem, for how do young cuttlefish, which as adults depend largely on individual learning, survive the first few moves in the survival game? How do they learn what to eat and when to run away? The answer is a rather curious one. It seems that cephalopods start life with some built-in recognition of situations. . . . Instead of . . . having innate responses fitted into the parents so that they shall recognise and protect their own young, the restrictions are fitted into the young, one generation later, so that it protects itself. As a parent faced with a further nineteen years of protective responsibility, I sometimes wonder whether the cuttlefish has not evolved a rather better answer to the whole problem."—MARTIN WELLS, *Listener*, Jan. 5, 1961; p. 16.

# TERSAVID IN ANGINA PECTORIS

## A Sequential Clinical Trial

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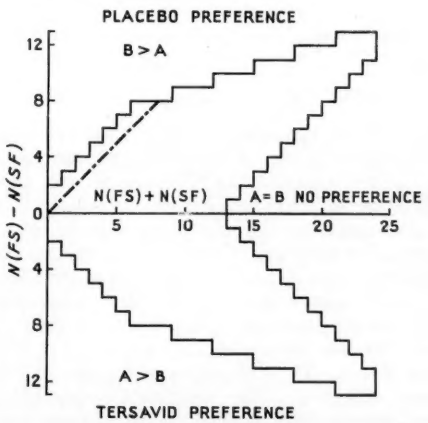
THE value of long-acting drugs in the relief of angina pectoris is difficult to assess. The advantages of using a double-blind technique have been stressed by many workers, including Katz (1956) and Shoshkes et al. (1959). In a previous trial of 'Tersavid' (1-benzyl-2-pivaloylhydrazine), 26 patients were treated for an average of six weeks using a dose of 50–75 mg. three times a day (Murphy and Barber 1960). Of these, 21 (65%) improved somewhat; and, in all but 4, the improvement was considerable. Side-effects were few and trivial. These results warranted further study of tersavid.

### Method

A restricted sequential procedure (Armitage 1957), arbitrarily limited to a maximum of 25 pairs, was chosen with a type-I error of 5% and a type-II error of 20%. The design was based on the assumption that the response-rate of those treated with the placebo would be 35%, and was constructed to indicate, with the minimum number of cases, a significant difference of about 35% between the two response-rates ($\theta_1=0·80$).

Outpatients with moderate or severe angina (Murphy and Barber 1960) were included in the trial. Patients were grouped in pairs, each pair being matched according to age, sex, and severity. Different treatments were randomly allocated to each member of a pair, using a code known only to the pharmacist. The treatments were tersavid and a placebo (glucose), coded A and B respectively. Each member of a pair was treated with two of the specified tablets four times a day for a four-week period. This gave a tersavid dose of 400 mg. daily. Patients were seen initially and then at fortnightly intervals by the same physician. At the end of the eight-week period, each patient was classified as S for success if the frequency of anginal attacks had been reduced by 50% or more, or F for failure in all other cases. The untied pairs, SF and FS, were plotted serially on the sequential graph (see figure) as the results became known; tied pairs, SS and FF, were not included.




**Sequential graph of trial of tersavid v. a placebo**

TABLE I—CHARACTERISTICS AND RESPONSES OF MATCHED PATIENTS TREATED WITH TERSAVID (A) AND A PLACEBO (B)

| No. | Sex | Age (yr.) | Severity | Result | Treatment |
|---|---|---|---|---|---|
| 1 | M | 59 | + + | F | A |
| | M | 64 | + | S | B |
| 2 | F | 42 | + + | F | A |
| | F | 74 | + + + | S | B |
| 3 | F | 68 | + + | S | B |
| | F | 73 | + + + | F | A |
| 4 | M | 59 | + + | F | A |
| | M | 51 | + | S | B |
| 5 | F | 74 | + + | S | B |
| | F | 66 | + + | S | A |
| 6 | F | 63 | + | S | B |
| | F | 55 | + | S | A |
| 7 | M | 59 | + + | F | A |
| | M | 52 | + + + | F | B |
| 8 | M | 54 | + | S | A |
| | M | 65 | + | S | B |
| 9 | M | 65 | + + + | S | B |
| | M | 59 | + + + | F | A |
| 10 | M | 59 | + + | S | B |
| | M | 61 | + + | F | A |
| 11 | M | 60 | + + | S | B |
| | M | 54 | + + | F | A |
| 12 | F | 56 | + + | F | A |
| | F | 54 | + + | F | B |
| 13 | M | 57 | + + | S | B |
| | M | 57 | + + | S | A |
| 14 | M | 59 | + + | F | A |
| | M | 57 | + + | S | B |
| 15 | M | 61 | + | S | B |
| | M | 42 | + | S | A |

## Results

Table I shows the outcome of the trial in the first 15 matched pairs.

The difference between the number of untied pairs, FS, SF, was plotted against their sum—i.e.,

$$N(FS) - N(SF) \text{ } v. \text{ } N(FS) + N(SF)$$

where, as in fig. 1, N(FS) represents the number of pairs in which the person treated with tersavid (A) was classed as a failure (F) and the person treated with the placebo was classed as a success (S). After only 8 untied pairs were recorded, the resultant line intersected the upper boundary in the figure. The trial was therefore stopped. 1 pair (no. 15), recorded after the trial ended, resulted in a tie (table I).

On breaking the code, the response-rate was found to be significantly greater in those treated with the placebo than in those treated with tersavid. Indeed, as can be seen from table I, when a difference occurred in the paired outcomes these were always of the type: failure to respond to A (tersavid) and response to B (placebo).

When the 15 pairs of results were classified by response to treatment (table II), the response-rate to the placebo (13/15)

TABLE II—CLASSIFICATION BY RESPONSE TO TREATMENT

| Treatment | Response | | |
|---|---|---|---|
| | Success | Failure | Total |
| Tersavid (A) .. .. .. .. | 5 | 10 | 15 |
| Placebo (B) .. .. .. .. | 13 | 2 | 15 |
| Total .. .. .. .. | 18 | 12 | 30 |

$\chi^2 = 8{\cdot}9$. Degrees of freedom = 1. $P < 0{\cdot}01$.

was shown to be significantly greater than the response-rate to tersavid (5/15). If the response-rate (33%) to tersavid is compared with the 35% response-rate expected for a placebo—which, in fact, was seriously underestimated—it is clear that tersavid would appear to be no better than a placebo. The matching of pairs by age, sex, and severity was checked to see if there was any bias in the allocation of subjects to pairs or to treatments. Both sexes appeared to react similarly since the 5 pairs of women yielded 2 SF, 2 SS, and 1 FF, compared with 6 SF, 4 SS, and 0 FF from the 10 pairs of men. The differences in the ages of the pair members did not differ significantly ($P > 0{\cdot}1$) and, similarly, the age differences of the untied pairs were not significant ($P > 0{\cdot}3$).

## Summary and Conclusions

In a double-blind trial of 'Tersavid', patients with angina pectoris were matched for age, sex, and severity; and were randomly allocated either active or inert treatment. The trial was carried out sequentially, and stopped as soon as a decision was reached.

The 30 recorded responses indicated that: (1) tersavid appeared to be less effective than a placebo; (2) the response-rate for tersavid (33%) was comparable with the expected response-rate for a placebo (35%), and both were significantly less than the observed placebo-response-rate (87%); and (3) no side-effect or other cause could be postulated which would explain the relative response levels in the two treatments.

At a dose of 100 mg. four times a day, tersavid is shown to be no better than a placebo in the relief of angina.

We are indebted to Mrs. D. Hutton for preparing the typescript and to Miss B. Thornbury for drawing the figure.

REFERENCES

Armitage, P. (1957) *Biometrika*, **44**, 9.
Katz, L. N. (1956) *Ann. N.Y. Acad. Sci.* **64**, 505.
Murphy, F. M., Barber, J. M. (1960) *Cardiologia, Basle*, **37**, 117.
Shoshkes, M., Rothfield, E. L., Becker, M. C., Finkelstein, A., Smith, C. C., Wachtel. F. W. (1959) *Circulation*, **20**, 17.

# LACTIC DEHYDROGENASE IN RENAL DISEASE

## Urinary Concentrations and Relative Clearances

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THE urinary excretion of lactic dehydrogenase (L.D.H.) in renal disease has been discussed by Rosalki and Wilkinson (1959). They suggested that the enzyme entered the urine as a result of cellular breakdown in the renal parenchyma, and that its level may therefore be a measure of such damage. I now report further investigations into this hypothesis, and put forward an alternative explanation for the increased amount of this enzyme in the urine of patients with proteinuria.

## Methods

All urine samples were timed 4-hour collections, free from preservative, and were examined on the day of collection. Calculated $^1/_{20}$ of 4 hour volumes were centrifuged; the supernatant was used for the enzyme determination, and the deposit for an Addis count (Addis 1948). The urinary L.D.H. (U.L.D.H.) and serum-L.D.H. (S.L.D.H.) were both determined by the spectrophotometric method of Wroblewski and La Due (1955) using 0·2 ml. of serum or centrifuged urine. All urine samples contained less than 0·5 mg. per 100 ml. of free hæmoglobin, as measured by the method of Bing and Baker (1931). Total proteins (serum and urine) were estimated by a modified biuret method (Wolfson et al. 1948), differential proteins by paper electrophoresis (Hardwicke 1954), and siderophilin by a gel-diffusion precipitin technique (Gell 1957).

## Results

102 samples from 58 cases have been examined. These cases comprise: nephrotic syndrome (as defined by Squire et al. 1957), 51 cases; undiagnosed proteinuria, 4; hæmaturia, 1; and 2 with a provisional clinical diagnosis of renal disease but no biochemical abnormality. The results of 51 samples from 25 cases where the diagnosis had been established by renal biopsy are summarised in table I.

TABLE I—RELATION BETWEEN HISTOLOGICAL CLASSIFICATION AND MEAN L.D.H. AND ALBUMIN CLEARANCES IN 25 CASES OF RENAL DISEASE

| Histological classification | Cases | S.L.D.H. (units per ml.) | U.L.D.H. ($\times 10^{-3}$ units per day) | L.D.H. clearance (ml. per min.) | Proteinuria (g. per day) | Albumin clearance (ml. per min.) |
|---|---|---|---|---|---|---|
| Minimal change | 5 | | | | | |
| Mean | | 24·2 | 19·2 | 0·07 | 3·9 | 0·04 |
| S.D. of mean | | 9·4 | 11·6 | 0·04 | 2·9 | 0·05 |
| Range | | 14·0–38·7 | 1·1–30·0 | 0·02–0·13 | 0·1–7·5 | 0·02–0·25 |
| Total | | (5) | (5) | (5) | (5) | (3) |
| Membranous change | 5 | | | | | |
| Mean | | 24·0 | 73·2 | 0·30 | 11·9 | 0·32 |
| S.D. of mean | | 7·8 | 46·0 | 0·35 | 5·0 | 0·17 |
| Range | | 17·2–42·0 | 2·8–180·0 | 0·01–1·52 | 2·5–24·2 | 0·03–0·59 |
| Total | | (16) | (16) | (16) | (16) | (14) |
| Proliferative change | 14 | | | | | |
| Mean | | 26·5 | 45·3 | 0·13 | 8·1 | 0·24 |
| S.D. of mean | | 8·8 | 31·6 | 0·08 | 8·4 | 0·24 |
| Range | | 13·0–52·0 | 2·7–114·7 | 0·001–0·32 | 0–29·6 | 0·01–0·79 |
| Total | | (30) | (30) | (30) | (30) | (21) |

S.L.D.H. = serum-lactic dehydrogenase. U.L.D.H. = urinary lactic dehydrogenase.

U.L.D.H. levels have been compared with S.L.D.H. levels, with total proteinuria, and with urinary red-cell counts. L.D.H.-clearance values were also calculated, and compared with albumin and siderophilin clearances.

## Discussion

Significant correlations (table II) have been demonstrated between U.L.D.H. and total proteinuria, as well as between L.D.H. clearance and albumin clearance, and to a lesser degree siderophilin clearance. This suggests that the enzyme, being a protein, is handled by the kidney in the same way as other proteins. The comparison between L.D.H. clearance and albumin clearance gives a ratio of 70/100, suggesting a molecular weight for L.D.H. of the order of 140,000 (Blainey et al. 1960). Meister (1950) found that the molecular weight for L.D.H. lies between 100,000 and 150,000.

TABLE II—ANALYSIS OF RELATIONSHIPS BETWEEN LACTIC DEHYDROGENASE AND OTHER FACTORS IN RENAL DISEASE

| — | Number of analyses | Correlation coefficient | P |
|---|---|---|---|
| U.L.D.H. and S.L.D.H. | 98 | 0·164 | >0·10 |
| U.L.D.H. and proteinuria | 97 | 0·688 | <0·001 |
| U.L.D.H. and urinary R.B.C. | 97 | 0·094 | >0·10 |
| L.D.H. clearance and albumin clearance | 61 | 0·445 | <0·001 |
| L.D.H. clearance and siderophilin clearance | 27 | 0·35 | 0·05–0·10 |

4 results from one case have been excluded—see text.

The permeability of the kidney to proteins of different molecular size is known to vary from one case to another, and within the same case at different stages of renal disease (Blainey et al. 1960). Hence, the S.L.D.H. and U.L.D.H. levels are not being compared in a homologous system, which explains the lack of correlation between them. This is also shown in table I. The mean S.L.D.H. level is similar in each of the histological groups, but the mean U.L.D.H. level varies, being highest with membranous change. These differences only reach statistical significance when comparing the proliferative and membranous groups, as the number of cases with minimal change was small. The mean L.D.H. clearance, therefore, differs between these groups, being greatest with membranous change, least with minimal change, and intermediate with proliferative change. This order of selectivity agrees with that found by Blainey et al. (1960) for other serum-proteins.

Figs. 1 and 2 show the relations that gave significant correlations—namely, between U.L.D.H. and proteinuria,

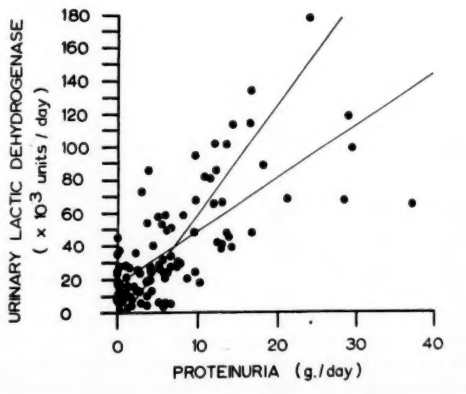


Fig. 1—Relation between urinary lactic-dehydrogenase concentrations and proteinuria.

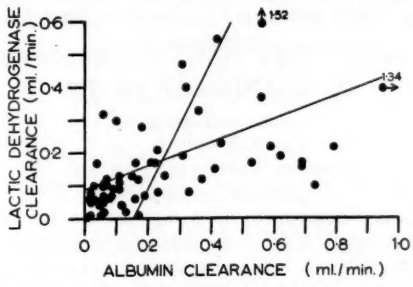


Fig. 2—Relation between calculated lactic-dehydrogenase clearance and albumin clearance.

and between L.D.H. clearance and albumin clearance. The two possible regression lines are shown for each relation. On the assumption that errors in the two parameters are of the same size, the functional relationship may be assumed to lie roughly midway between the regression lines. In this way, total L.D.H. clearance has been calculated to be 70% of the albumin clearance on average.

The lack of agreement between U.L.D.H. and urinary red-cell counts—which are frequently taken as an index of active renal damage—suggests that there is no relation between U.L.D.H. levels and, at any rate, those types of renal lesion associated with hæmaturia.

The four results which were excluded in the calculations summarised in table II were all from one case of proliferative glomerulonephritis. The U.L.D.H. was consistently raised (72·7 to 760·8 $\times 10^{-3}$ units per day), the proteinuria moderate

(2·9 to 5·2 g. per day), and the albumin clearance low (0·02 to 0·06 ml. per min.). The urine was always purulent; and the great excess of pus cells might be responsible for the high U.L.D.H. concentrations. This was the only case of its kind met in the present series.

In my opinion, these results suggest that, in renal disease, L.D.H. is excreted in the urine in the same manner as any other protein. They seem to refute the views of Rosalki and Wilkinson (1959) that U.L.D.H. is a measure of renal parenchymal damage—at least in patients with the nephrotic syndrome.

**Summary**

Urinary lactic dehydrogenase has been measured and compared with serum-lactic dehydrogenase, with proteinuria, and with urinary red-cell counts. Lactic dehydrogenase clearances have been calculated and compared with albumin and siderophilin clearances.

In renal disease lactic dehydrogenase appears to be handled by the kidney as a protein of medium molecular weight and excreted as such.

No correlation has been found between urinary lactic dehydrogenase and urinary red-cell counts.

My thanks are due to Prof. J. R. Squire for encouragement to publish this work, to Dr. John Hardwicke for his help and interest, and to Dr. J. F. Soothill for permission to use the siderophilin clearance results.

REFERENCES

Addis, T. (1948) Glomerular Nephritis; p. 10. New York.
Bing, F. C., Baker, R. W. (1931) *J. biol. Chem.* **92**, 589.
Blainey, J. D., Brewer, D. B., Hardwicke, J., Soothill, J. F. (1960) *Quart. J. Med.* **29**, 235.
Gell, P. G. H. (1957) *J. clin. Path.* **10**, 67.
Hardwicke, J. (1954) *Biochem. J.* **57**, 166.
Meister, A. (1950) *J. biol. Chem.* **184**, 117.
Rosalki, S. B., Wilkinson, J. H. (1959) *Lancet*, ii, 327.
Squire, J. R., Blainey, J. D., Hardwicke, J. (1957) *Brit. med. Bull.* **13**, 43.
Wolfson, W. Q., Cohn, C., Calvery, F., Ichiba, F. (1948) *Amer. J. clin. Path.* **18**, 723.
Wroblewski, F., La Due, J. S. (1955) *Proc. Soc. exp. Biol., N.Y.* **90**, 210.

# A SLIDE TEST FOR THE DIAGNOSIS OF GLANDULAR FEVER

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THE agglutination of sheep erythrocytes by patient's serum is used as an aid in the diagnosis of glandular fever (Paul and Bunnell 1932). Because this "presumptive" test is not specific, the differential absorption test is usually done at the same time (Davidsohn et al. 1951). The latter, however, is time-consuming, and in order to avoid performing it in every suspected case of glandular fever many "screening" procedures have been introduced.

Wollner (1955) found that a proteolytic enzyme, papain, specifically inactivated receptors for the antibodies of glandular fever on sheep erythrocytes, which could then be tested at the same time with the presumptive test, obviating the need for the differential absorption tests. Springer and Rapaport (1957) and Muschel and Piper (1959) have confirmed these findings.

This paper describes a simple slide test designed for the diagnosis of glandular fever, using native and papain-treated sheep erythrocytes.

## Material and Methods

*Sheep erythrocytes* from defibrinated blood were used, 1 to 6 days after bleeding; they were washed three times in 5 volumes of isotonic saline. 20% and 2% saline suspensions were then made from packed washed erythrocytes and used within 2 hours of preparation for slide, presumptive, and differential absorption tests.

Sheep erythrocytes stored in Lock's solution were also tested after being washed three times.

*Papain* was made according to Löw's (1955) technique with slight modifications: 2 g. of papain (British Drug Houses) was ground in a mortar with 100 ml. of *M*/15 Sørensen phosphate buffer, pH 5·4, after which the suspension was filtered. 5 ml. of *M*/1 *l*-cysteine hydrochloride was brought to neutral point with *M*/1 NaOH (approximately 5 ml.); 10 ml. of this neutralised solution was then added to the papain solution and the whole made up with buffer to 200 ml., incubated at 37°C for 1 hour, dispensed into 1 ml. aliquots, and stored at −20°C. Thus prepared, the papain will not lose any significant amount of activity for at least 12 months. Once thawed, it must be used within a few hours; it will not tolerate refreezing or rethawing. Before use, the papain is diluted with 1 volume of buffered isotonic sodium chloride (NaCl 9 g., $Na_2HPO_4$ 1·36 g., and $NaH_2PO_4.2H_2O$ 0·24 g. dissolved in 1 litre of distilled water), thus making a final enzyme dilution of 1/200, at pH 6–7.

*Preparation of sera.*—Freshly collected blood was allowed to clot. Serum was obtained by centrifugation and, unless immediately tested, stored at −20°C until used. For the presumptive and differential absorption tests, sera were inactivated for 30 minutes at 56°C. For the slide test, the results were the same whether native or inactivated sera were used.

### *The Slide Test*

The test is performed at room temperature. A drop of a 20% suspension of washed sheep erythrocytes is placed on each end of a clean dry microscope slide. A drop of papain solution is mixed with one, and a drop of physiological saline with the other; the slide is left to stand for 3 minutes. One drop of serum is then added to each drop of native and papain-treated sheep erythrocytes, and the stopwatch started. The slide is rocked gently and the time recorded when macroscopic hæmagglutination is observed.

### *Presumptive and Differential Absorption Tests*

The presumptive and differential absorption tests were done according to the method of Davidsohn (1938), as described by Cartwright (1958). Instead of reading the agglutination

TABLE I—SEROLOGICAL INVESTIGATIONS AND SLIDE TESTING ON PATIENTS WITH GLANDULAR FEVER

| Serum | Presumptive-test titre | Titre after absorption with | | Slide test with sheep erythrocytes | |
|---|---|---|---|---|---|
| | | Guineapig kidney | Beef erythrocytes | Native (seconds) | Papain-treated (seconds) |
| 1 | 224 | 224 | <7 | 30 | 80 |
| 2 | 448 | 224 | <7 | 20 | 110 |
| 3 | 224 | 112 | <7 | 40 | >120 |
| 4 | 448 | 448 | <7 | 20 | >120 |
| 5 | 448 | 448 | 7 | 40 | >120 |
| 6 | 448 | 224 | 7 | 37 | >120 |
| 7 | 896 | 896 | 7 | 20 | 67 |
| 8 | 224 | 224 | 7 | 30 | >120 |
| 9 | 112 | 112 | <7 | 50 | 110 |
| 10 | 112 | 112 | 7 | 33 | >120 |
| 11 | 896 | 224 | <7 | 24 | >120 |
| 12 | 112 | 112 | 7 | 23 | 70 |
| 13 | 224 | 224 | 14 | 25 | >120 |
| 14 | 896 | 896 | 7 | 23 | 50 |
| 15 | 112 | 56 | 7 | 40 | >120 |
| 16 | 448 | 448 | 7 | 35 | >120 |
| 17 | 448 | 448 | <7 | 20 | >120 |
| 18 | 448 | 448 | <7 | 19 | >120 |
| 19 | 896 | 448 | 28 | 30 | >120 |
| 20 | 56 | 56 | <7 | 42 | >120 |
| 21 | 896 | 896 | <7 | 26 | >120 |
| 22 | 56 | 56 | <7 | 50 | 85 |
| 23 | 448 | 224 | 14 | 8 | 28 |
| 24 | 56 | 28 | <7 | 22 | 55 |
| 25 | 1792 | 1792 | 7 | 16 | >120 |
| 26 | 448 | 448 | 14 | 30 | >120 |
| 27 | 896 | 448 | <7 | 33 | 110 |
| 28 | 112 | 112 | 7 | 13 | 28 |

TABLE II—SEROLOGICAL INVESTIGATIONS AND SLIDE TESTING ON PATIENTS SUSPECTED OF HAVING GLANDULAR FEVER

| Serum | Presumptive-test titre | Titre after absorption with | | Slide test with sheep erythrocytes | |
|---|---|---|---|---|---|
| | | Guineapig kidney | Beef erythrocytes | Native (seconds) | Papain-treated (seconds) |
| 1 | 28 | <7 | 7 | >120 | 80 |
| 2 | 56 | 7 | 14 | 80 | 45 |
| 3 | 448 | 14 | 112 | 50 | 38 |
| 4 | 7 | <7 | 7 | >120 | >120 |
| 5 | 112 | <7 | 56 | 65 | 50 |
| 6 | <7 | <7 | <7 | >120 | >120 |
| 7 | 56 | 7 | 28 | 120 | 85 |
| 8 | 56 | <7 | 28 | 90 | 65 |
| 9 | 14 | 7 | 7 | >120 | 50 |
| 10 | 56 | 14 | 28 | >120 | 40 |
| 11 | 28 | 7 | 14 | >120 | 46 |
| 12 | 56 | <7 | 56 | 65 | 24 |
| 13 | 28 | 7 | 14 | 68 | 30 |
| 14 | 7 | <7 | 7 | >120 | >120 |
| 15 | 7 | <7 | 7 | >120 | >120 |
| 16 | 28 | 7 | 7 | >120 | 52 |
| 17 | 112 | 7 | 56 | >120 | 45 |

reaction after 2 hours' incubation at room temperature, the modification of Zafronetis et al. (1953) was used—i.e., incubation at 4°C overnight and, after resuspension, incubation at 37°C for 2 hours, after which agglutination figures were recorded as highest dilutions of sera giving agglutinations clearly visible to naked eye.

## Results

Table I presents results of investigations done on patients diagnosed as having glandular fever on clinical, hæmatological, and serological grounds. In the slide test, the papain-treated sheep erythrocytes always showed a delay in the onset of agglutination by at least 15 seconds when compared with native erythrocytes.

The reverse was seen with the sera of patients in whom the suspected clinical or hæmatological diagnosis of glandular fever could not be substantiated on serological grounds (table II), when the papain-treated sheep erythrocytes showed agglutination earlier than native erythrocytes.

Sheep erythrocytes stored in Lock's solution gave slightly different results. When compared with saline-stored cells, the agglutination times were 10–20 seconds shorter with both native and papain-treated erythrocytes.

The slide test was carried out on 68 normal sera, and on 302 sera from patients with various diseases. When hæmagglutination was observed, it was almost always seen first in papain-treated sheep erythrocytes, and very seldom in native cells during the observation period of 120 seconds. Whenever agglutination occurred in both papain-treated and native sheep erythrocytes, there was a delay of at least 10 seconds in the onset of agglutination in native cells, as compared with those treated with papain. Agglutination with sera from normal controls was seen in about 1% of cases, whereas in the group of patients with various diseases it was observed in about 8% of cases of acquired immune hæmolytic anæmia, undiagnosed febrile illnesses, and hypersensitivity conditions.

Because it has been shown (Zagronetis and Oster 1950) that there is wide variation in the agglutination properties of erythrocytes from various sheep, erythrocytes obtained from various sheep were tested against same serum samples. A difference in agglutinability varying by only 5 seconds with native cells in the slide test was noted; with papain-treated cells, however, a difference of up to 10 seconds was observed. In both tables I and II, only the smallest differences in agglutination times with various sheep erythrocytes are recorded.

Bromelin, a proteolytic enzyme obtained from pineapple, prepared by the method of Pirofsky (1959) was tried as a substitute for papain in the slide test; the results were disappointing and there was no agreement with those from papain-treated cells.

Analysis of results from tables I and II shows complete agreement between the slide test and the standard absorption test. It is also apparent from table II, and from slide tests carried out on normals as well as patients with a variety of illnesses, that heterophil antibodies other than those of glandular fever are readily demonstrable on papain-treated sheep erythrocytes.

The present slide test is based on the screening procedure of Brumfitt and O'Grady (1957), and except for one serum (serum no. 5, table II) this study confirms their results—namely, that if agglutination on the slide occurred within 60 seconds, the presumptive-test titre would be 1/80 or higher. The introduction of papain-treated sheep erythrocytes, however, makes the test best specific for glandular fever.

## Summary

A simple slide test for diagnosis of glandular fever is described. At the same time the test will reveal the presence of other heterophil antibodies, thus obviating the need for the specific absorption test.

I am indebted to Dr. R. D. K. Reye, director, and to Mr. D. C. Dorman, bacteriologist, Institute of Pathology, Royal Alexandra Hospital for Children, for their constructive criticism of this paper.

REFERENCES

Brumfitt, W., O'Grady, F. (1957) *J. clin. Path.* **10**, 243.
Cartwright, G. E. (1958) Diagnostic Laboratory Hematology; p. 241. New York.
Davidsohn, I. (1938) *Amer. J. clin. Path.* **8**, 56.
— Stern, K., Kashiwagi, C. (1951) *ibid.* **21**, 1101.
Löw, B. (1955) *Vox Sanguinis*, **5**, 94.
Muschel, L. M., Piper, D. R. (1959) *Amer. J. clin. Path.* **32**, 240.
Paul, J. R., Bunnell, W. W. (1932) *Amer. J. med. Sci.* **183**, 90.
Pirofsky, B. (1959) *Amer. J. clin. Path.* **32**, 350.
Springer, G. F., Rapaport, N. J. (1957) *Proc. Soc. exp. Biol.* **96**, 103.
Wollner, D. (1955) *Z. ImmunForsch.* **112**, 290.
Zafronetis, C. J. D., Oster, H. L. (1950) *J. Lab. clin. Med.* **36**, 283.
— — Eloise, M., Colville, V. F. (1953) *ibid.* **41**, 906.

# PEMPIDINE

## A Ganglion-blocking Drug for Treating Hypertension

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DRUGS with a selective action on the sympathetic nervous system are not yet established as the best method of lowering the blood-pressure, and interest in new ganglion blocking agents continues.

In 1956 mecamylamine was introduced and claims were made that, owing to better absorption, the effects of the drug were more predictable than others, and that its action was smoother and more prolonged. However, in our experience (Kitchin, Lowther, and Turner 1957), mecamylamine, although possibly the best of the ganglion-blocking drugs, produced tolerance and troublesome side-effects from parasympathetic blockade. Its apparent advantages over other preparations were not sufficient to justify controlled trials on patients with severe hypertension.

In 1958 a new ganglion-blocking agent, pempidine tartrate, was made available under the trade names of

'Perolysen' and 'Tenormal' and its pharmacological properties were described by Spinks and Young (1958) and by Harington et al. (1958). This substance has the formula 1:2:2:6:6-pentamethylpiperidine and is structurally related to mecamylamine ('Inversine'), but differs from it in certain respects which some thought might make it a more effective hypotensive agent. Harington et al. (1958) concluded that its more rapid and complete excretion should enable the dose to be increased more quickly, and with greater safety, at the beginning of treatment; and they hoped that serious side-effects might be shortlived and more easily treated.

We have carried out a pilot trial to see whether these theoretical advantages did provide better and safer results in practice, whether the blood-pressure could be adequately controlled, and whether the incidence of side-effects was less than that produced by other ganglion-blocking substances.

## Patients and Method

Pempidine was given to 18 consecutive patients who were judged to require hypotensive therapy according to the criteria laid down for treatment with mecamylamine (Kitchin et al. 1957). Raised blood-pressure levels were treated only if accompanied by evidence of secondary hypertensive disease, or if severe hypertension was found in young persons. The same procedure of inpatient assessment and stabilisation of treatment, and then discharge from the wards to a special outpatient clinic, was followed. Table I gives brief clinical details of the patients treated, together with the casual blood-pressures recorded in the outpatient department, and resting pressures recorded in bed. As with other hypotensive agents, satisfactory control of the blood-pressure often led to alleviation of symptoms, regression of hypertensive retinopathy, and return towards normal of the electrocardiographic pattern of left ventricular hypertrophy; but

TABLE I—DATA ON 18 PATIENTS TREATED

| Patient | Age | Sex | Major symptom | Fundi | Electro-cardio-gram | Renal function | Blood-pressure (mm. Hg) | | | Daily dose (mg) | Total length of treatment (mos.) | Result (based on blood-pressure) | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Initial | Resting | Stabilisation | | | | |
| 1 | 41 | F | Headache | III | L.V.H. | Imp. | 260/135 | L. 260/135<br>S. 240/135 | L. 190/105<br>S. 130/85 | 15 | 4 | Good | Œdema from reduced glomerular filtration-rate. Dose reduced and chlorothiazide added. Good control of blood-pressure, but troublesome side-effects. Died from unrelated disease |
| 2 | 53 | M | Angina<br>C.V.A. | IV | L.V.H. | N | 260/150 | L. 240/135<br>S. 225/135 | L. 230/125<br>S. 180/110 | 30 | 7 | Fair | Initial good control, but troublesome side-effects. Drug changed |
| 3 | 55 | M | L.V.F. | II | L.V.H. | N | 225/135 | L. 200/110<br>S. 190/100 | L. 170/115<br>S. 170/110 | 45 | 4 | Poor | Tolerance developed. Defaulted |
| 4 | 53 | M | L.V.F. | II | L.V.H. | N | 210/125 | L. 230/110<br>S. 205/125 | L. 230/135<br>S. 220/130 | 22·5 | 6 | Poor | Severe side-effects. Drug changed |
| 5 | 59 | F | L.V.F. | II | L.V.H. | Imp. | 250/120 | L. 220/110<br>S. 215/105 | L. 220/115<br>S. 170/90 | 37·5 | 7 | Good | Good control with minimal side-effects |
| 6 | 57 | F | L.V.F. | III | Early L.V.H. | N | 260/140 | L. 200/115<br>S. 180/115 | L. 210/115<br>S. 150/105 | 30 | 3 | Fair | Mild side-effect, but frequent postural hypotension. Drug changed |
| 7 | 44 | F | C.V.A. | II | L.V.H. | N | 250/140 | L. 200/120<br>S. 195/125 | L. 200/120<br>S. 135/100 | 30 | 8 | Fair | Fair control. Severe side-effects. Drug changed |
| 8 | 55 | M | Headache | II | L.V.H. | N | 245/140 | L. 230/120<br>S. 220/135 | L. 165/105<br>S. 130/95 | 55 | 18 | Good | Good control. Moderate side-effects. Drug changed |
| 9 | 42 | M | C.V.A. | II | L.V.H. | N | 180/115 | L. 170/110<br>S. 180/115 | L. 150/115<br>S. 125/95 | 30 | 6 | Good | Good control. Severe side-effects. Drug changed |
| 10 | 42 | F | C.V.A. | III | L.V.H. | N | 260/150 | L. 225/150<br>S. 210/140 | L. 200/135<br>S. 135/95 | 75 | 7 | Good | Good initial control with mild side-effects. Tolerance. Drug changed |
| 11 | 42 | F | Epitaxis | II | L.V.H. | N | 230/130 | L. 215/120<br>S. 195/120 | L. 180/110<br>S. 130/95 | 52·5 | 9 | Good | Good control with mild side-effects |
| 12 | 49 | M | C.V.A. | IV | B.B.B. | N | 240/145 | L. 220/145<br>S. 210/145 | L. 160/105<br>S. 120/95 | 30 | 5 | Good | Good control with mild side-effects |
| 13 | 56 | F | C.V.A. | III | L.V.H. | N | 210/140 | L. 225/135<br>S. 210/130 | L. 200/125<br>S. 135/105 | 22·5 | 2 | Fair | Severe side-effects. Drug changed |
| 14 | 57 | M | .. | I | L.V.H. | N | 230/125 | L. 210/115<br>S. 200/115 | L. 170/100<br>S. 120/90 | 22·5 | 1 | Good | Good control, but endogenous depression led to withdrawal of treatment |
| 15 | 55 | M | Angina | III | L.V.H. | N | 270/140 | L. 240/130<br>S. 230/135 | L. 215/125<br>S. 145/95 | 30 | 1 | Good | Good control, but severe side-effects. Drug changed |
| 16 | 59 | F | Headaches; dizziness | III | L.V.H. | N | 260/155 | L. 220/145<br>S. 210/140 | L. 210/145<br>S. 160/115 | 22·5 | 1·5 | Poor | Fair control with moderate side-effects. Drug changed |
| 17 | 48 | M | L.V.F. | IV | L.V.H. | Imp. | 250/150 | L. 260/155<br>S. 230/145 | L. 170/105<br>S. 110/80 | 22·5 | 2·5 | Good | Good control, but severe side-effects. Drug changed |
| 18 | 55 | F | Headache | II | L.V.H. | N | 230/120 | L. 240/125<br>S. 210/115 | L. ..<br>S. .. | 7·5 | .. | .. | Vomited with every dose in two trials. Drug changed and good control obtained |

B.B.B. = bundle-branch block; C.V.A. = cerebrovascular accident; L.V.F. = left ventricular failure; L.V.H. = left ventricular hypertrophy; Imp. = impaired renal function; N = normal renal function; L. = lying; S. = standing.

because of the short period over which most patients have been treated, a fall in blood-pressure has been taken as the sole criterion of therapeutic effect.

The aim of treatment was to reduce the standing diastolic pressure to as near normal as was compatible with freedom from hypotensive symptoms or undue side-effects. A " good " result was claimed if the pressure was reduced by 30/20 mm. or more provided the diastolic pressure was below 100 mm. If the pressure was lowered by 30/20 mm. and the diastolic pressure was reduced to 100–110 mm., a " fair " result was claimed. If the pressure could not be reduced significantly, the result was graded as " poor ". In addition, however, some patients showed a " temporarily good " result—i.e., a satisfactory fall in diastolic blood-pressure which could not be maintained for more than a few weeks without disabling side-effects.

Pempidine was given after meals, the initial dose being 2·5 mg. three times daily. Each dose was increased by 2·5 mg. at intervals of two or three days.

Because the fall in blood-pressure mainly depends on posture, we felt that control during the waking period is all that can be expected of ganglion-blocking drugs. We have found that drugs of this type usually exert a slight effect on the lying pressure, but even this is not seen in all patients. Also, we may fairly assume that at night, during sleep, the pressure is relatively low.

When a stable and satisfactory fall in blood-pressure had been obtained, the patients were discharged to the outpatient clinic. If the pressure subsequently tended to rise, the dose was further increased. As with other ganglion-blocking drugs, dosage may be critical and a small increment may result in severe postural hypotension. In some patients control could not be regained without severe side-effects developing. In others, only partial control was achieved. In 1 patient, tolerance necessitated a repeated increase in dose.

In 7 cases chlorothiazide was used in addition to pempidine because it is a potent adjuvant to ganglion-blocking drugs. In 3 of these, it was used because the blood-pressure could not otherwise be maintained at the desired level. In 3 cases chlorothiazide was added where renal damage was known to be present or where a fall in renal blood-flow had given rise to peripheral œdema. In 1 case it was added to allow a reduction of pempidine because the patient was having difficulty in micturition.

When chlorothiazide was given to patients already taking pempidine, the dose of the latter was initially halved in order to avoid the precipitous drops of pressure to which we have previously drawn attention (Kitchin et al. 1958).

## Results

The results presented will be confined to observations on the ability of the drug to produce and maintain a satisfactory fall in blood-pressure without disabling side-effects from parasympathetic blockade.

12 patients continued with the drug for six to eighteen months (average of nine months). 6 patients (13–18 in table I) took the drug for less than three months, and were then changed to bretylium tosylate (' Darenthin ') because it became clear that the side-effects of pempidine were no different in character or severity from those of other ganglion-blocking drugs.

The total daily dose of pempidine varied between 10 and 75 mg., with a mean of 30 mg. The last patient in the series vomited persistently as soon as she was given the first daily dose of 7·5 mg. of pempidine, and this side-effect recurred after a second trial of the same dose, but cleared up when the patient was given mecamylamine. For this reason, no hypotensive effect could be recorded and the patient appears only in the section concerned with side-effects.

Table I shows that considerable difficulty was encountered in maintaining a satisfactory blood-pressure response without undue side-effects. In 17 patients the initial response was good, but in 7 this was only temporary, 5 slipping back to " fair " and 2 to " poor " despite continued efforts. In 10 cases a good blood-pressure response was maintained throughout the period of observation but only at the cost of a high toll of discomfort from the side-effects summarised in table II. In 7 patients, including 3 classified as " good " as far as a fall in blood-pressure was concerned, side-effects were so disabling that the drug was stopped. Thus pempidine has been a satisfactory clinical agent in only 7 cases.

Tolerance, requiring a steady increase in dosage, was found in 1 patient.

## Side-effects

These side-effects (table II) follow the familiar pattern of parasympathetic blockade, and the remedies prescribed were similar to those advised for mecamylamine (Kitchin et al. 1957).

TABLE II—SIDE-EFFECTS (18 PATIENTS)

| — | Total | Severe |
|---|---|---|
| Constipation | 18 | 5 |
| Dry mouth | 13 | 5 |
| Visual disturbance | 9 | 3 |
| Malaise | 6 | 3 |
| Postural hypotension | 4 | 1 |
| Difficulty in micturition | 2 | 2 |

2 patients had retention of urine. In 1, a reduction in the dose of pempidine together with the addition of chlorothiazide was effective; and in the other, mecamylamine was substituted. As with other ganglion-blocking drugs very few patients felt really well on treatment.

Other adverse effects were those due to excessive sympathetic blockade and consisted of postural hypotension and, in 1 patient, of œdema from reduction of glomerular filtration.

## Conclusions

Though there is no doubt that pempidine is a potent ganglion-blocking agent, the same difficulties in practical administration have arisen which have rendered other drugs in this group unsatisfactory. We have been unable to show that pempidine tartrate is likely to prove any more (or less) effective or palatable than mecamylamine or pentolinium, and for this reason we cannot recommend it for controlled trials.

## Summary

A trial of pempidine tartrate in the treatment of 18 patients with severe hypertension is described. 1 could not tolerate the drug for long enough to produce a hypotensive effect; and of the remaining 17, satisfactory control of the diastolic blood-pressure at normal levels could be maintained in only 10. In 3 of these, severe side-effects led to subsequent withdrawal of the drug. In 7, after a temporary good response, control was lost and could not be regained.

Though there is no doubt of the ability of pempidine tartrate to reduce the blood-pressure, the drug offers no advantage over other ganglion-blocking substances.

## REFERENCES

Harington, M., Kincaid-Smith, P., Milne, M. D. (1958) *Lancet*, ii, 6.
Kitchin, A., Lowther, C. P., Turner, R. W. D. (1957) *ibid.* ii, 605.
— — — (1958) *Brit. med. J.* i, 1302.
Spinks, A., Young, E. H. P. (1958) *Nature, Lond.* **181**, 1397.

# New Inventions

## A BUTTRESS FOR SKIN-GRAFTING

THIS instrument (fig. 1) consists of a brass strip with a slot running at right angles from the edge to the centre near one end. The slot can be closed to a round hole with a button-operated slide, which runs in the edge of the handle.

In use, the slide is closed and the instrument is pressed along the margin of the defect, as illustrated (fig. 2), so supporting

**Fig. 1—The buttress.**
Length 14 cm.; width 1·4 cm.; thickness 2 mm.; slot 2 mm. wide at 1 cm. from end.

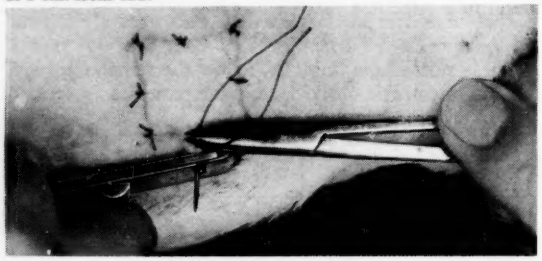

**Fig. 2—The buttress in use.**

it that a needle may be passed through the graft and the skin edge, and emerge through the slot. When the stitch is completed, the slide is retracted and the instrument is removed from round the thread. This avoids the crushing or tearing of skin margins which may occur where toothed forceps are used. The instrument is especially valuable where the margin of the defect is thick tough skin.

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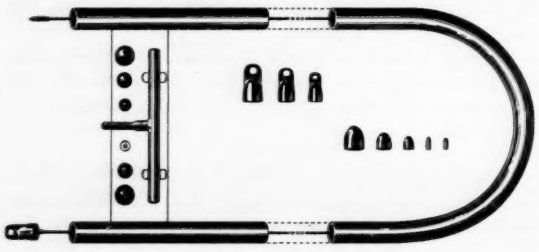
## A VARICOSE-VEIN STRIPPING SET

THE stripping of varicose veins has become established as an indispensable adjunct to the strategic flush ligation of the saphenofemoral and saphenopopliteal junctions. From time to time stripping presents technical difficulties, and sometimes these are due to previous treatment, such as injection and multiple ligature. It is necessary, therefore, to have instruments which lend themselves to stripping from above and below, and which have tips of various sizes to negotiate narrowed veins. Because the stripping shoulder at the distal end needs to be large enough for a large vein and small enough to cause very little trauma to smaller vessels, various-sized stripping shoulders are needed.

A stripper is an awkward instrument to contain in the steriliser, and on an instrument table it springs about and easily becomes unsterile; therefore a convenient holder has been made which will take several strippers, and various-sized tips and stripping shoulders. These are attached by screwing, so that sizes appropriate to the vein in question can be readily selected, and the tip and shoulder can be changed from one end to the other. Two types of stripping shoulders are available—the Myers half-acorn, and the cup-shaped. These are designed to assist stripping, with a key at the end for twisting and turning the instrument to facilitate its passage along a tortuous and



pouched vein. A handle makes the stripping-out easy. The outfit is easily contained by the steriliser, and can be conveniently lifted on to the instrument table.

The stripping set is made by A. L. Hawkins & Co., Ltd., of 15, New Cavendish Street, London, W.1, to whom I am indebted for its construction.

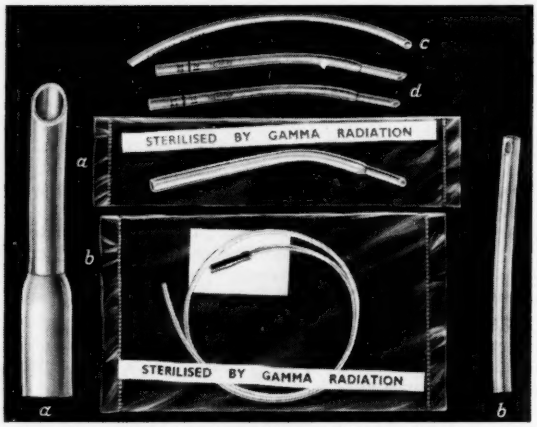
London, W.1

HAROLD DODD,
CH.M. Lpool, F.R.C.S.

## A STERILE DISPOSABLE NEONATAL TRACHEAL TUBE

ENDOTRACHEAL oxygenation has become a routine neonatal resuscitative procedure in many obstetric units.[1 2] Complications or infections due to this procedure are rare, but we have found that sterility is difficult to maintain, and random culture of the endotracheal tubes in our unit has, on occasion, shown organisms such as *Proteus vulgaris*, *Streptococcus fæcalis*, *Neisseria catarrhalis*, and *Staphylococcus pyogenes*. Progress towards sterility in this field is obviously desirable; and, because the cost of adequately cleaning, sterilising, and packaging a neonatal endotracheal tube is great, a disposable tube is preferable.

The packaged sterile endotracheal tube (see figure [*a*]), made of polyvinyl ' Riplex ', is disposable and designed for use primarily in resuscitation of the newborn. The endotracheal part of the tube, of 12 French gauge with a bore of 2·6 mm., is 2 cm. long and fused to the extratracheal portion in manufacture. Included in the figure is a sterile disposable suction catheter (*b*) of the same material, for use in conjunction with endotracheal suction through the tube. The internal ledge at the junction of the extratracheal and endotracheal portions of the tube causes no obstruction to the passage of the suction catheter if the latter is twisted backwards and forwards during insertion through the tube. Also in the figure for comparison are a 00 Magill




endotracheal tube (*c*) and two Porges ' Neoplex ' endotracheal tubes (*d*). This type of compound tube was first demonstrated many years ago by Sir Ivan Magill, and our tube is based on the plastic Cole tube.[3] An improved adaptation,[4] manufactured by the Foregger Company, has been used in our unit since 1956.

The suction catheter has been used successfully for exchange transfusion and for routine " cut-down " intravenous infusion in the ward. Preliminary observations in this unit suggest that these sterile disposable tubes are worthy of an extended trial in neonatal resuscitative procedures.

Both the tube and the catheter are obtainable from William Warne & Co., Ltd., India Rubber Mills, Barking, Essex.

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1. Hodges, R. J. H., Tunstall, M. E., Knight, R. F., Wilson, E. J. *Brit. J. Anæsth.* 1960, **32**, 9.
2. Abramson, H. Resuscitation of the Newborn Infant. St. Louis, 1960.
3. Cole, F. *Anesthesiology*, 1945, **6**, 87.
4. Cole, F. *ibid.* p. 627.

# Reviews of Books

## Obstetrical and Gynæcological Pathology for Post-graduate Students

R. E. REWELL, M.D., M.R.C.P., consultant pathologist, The Women's Hospital, Maternity Hospital and Ear, Nose and Throat Infirmary, Liverpool. Edinburgh: E. & S. Livingstone. 1960. Pp. 435. 50*s*.

THERE are now several textbooks of obstetric and gynæcological pathology, but it is a pleasure to find one in which the problems of obstetric pathology receive more than a passing mention. It is true that more than half of this book is concerned with gynæcological conditions, but there are also chapters on diseases of the placenta, maternal mortality and morbidity, blood-clotting defects, anæmia in pregnancy, and puerperal sepsis. Dr. Rewell has also included a chapter on perinatal mortality, including congenital abnormalities, and another on the problems of iso-immunisation.

He has succeeded in compressing much detail into small space without loss of fluency, and the book is very readable. A pleasing feature is the way he introduces material from his experience as professor of pathology in Madras under the Colombo Plan. Many students of obstetrics and gynæcology who are attending courses at postgraduate centres in this country come from overseas, and the standard textbooks tend to emphasise questions which often arise in Western Europe and the U.S.A. but which may be less important in the tropics. These differences are brought out in the chapters on carcinoma of the cervix and of the body of the uterus, chorionepithelioma, and iso-immunisation in pregnancy.

The author's approach inevitably makes the text of more interest to the clinician than to the pathologist; but the book will help those pathologists who may have to examine material from obstetric or gynæcological patients but who spend most of their time on other subjects.

One small criticism is that the description of the frequency and mode of spread in carcinoma of the body of the uterus could be clarified, and the views on the origin of the mixed tumours of the body of the uterus may not be universally accepted. The book is well illustrated: the 150 figures, mainly photomicrographs, are skilfully chosen and beautifully reproduced. There is a long bibliography, and many references are remarkably up-to-date. The production is of a high standard, and the book can be cordially recommended.

## Mental Health and Social Policy

KATHLEEN JONES, PH.D., lecturer in social administration (specialising in the teaching of mental-health administration), University of Manchester. London: Routledge and Kegan Paul. 1960. Pp. 237. 28*s*.

Dr. Jones' celebrated book, *Lunacy Law and Conscience*, describing developments in the care of the mentally ill between 1744 and 1845, made everyone hope that she would one day bring the story up to date. This she has now brilliantly done, and the new volume stands beside its predecessor as a classic. But the past 100 years have been quieter ones, so this book is much less stirring. There has been little to set beside Ashley's early battles or the dark doings at York asylum, for example.

Her account of the 1959 Act covers well-trodden ground, and her judgment on some current controversies suffers inevitably from brevity and closeness. Nor has she said the last word on the decline into institutionalism which was the tragedy of the late 19th century. The Act of 1890 was undoubtedly retrogressive, but whether it represented only the triumph of legalism which Dr. Jones describes is less clear. Undoubtedly the fear of wrongful detention led to stringent legal safeguards and delay in treatment, but the drop in the curve of progress (which was seen, too, in the U.S.A. and in the prisons) may have sprung from more basic reasons in the public mind, of which legalism was but a symptom. But as a piece of scholarship the book has all the merits of its forerunner—accuracy, elegant and concise language, and good indexing and documentation. Dr. Jones' grasp of the broad sweep of events over the century is remarkable, and the work deserves the widest study.

## Marshall's Physiology of Reproduction

3rd ed. Vol. 1, part 2. Editor: A. S. PARKES, C.B.E., M.A., D.SC., F.R.S., National Institute for Medical Research, London. London: Longmans, Green. 1960. Pp. 877. £12.

THE vast organism engendered by the late T. H. Marshall continues to reproduce by binary fission. The first part of the volume dealt with cycles of reproduction and genital morphology in the female; the new part deals with spermatogenesis, insemination, and fertilisation. In this field, to which its distinguished editor has made great contributions of his own, it could hardly fail to be informative, and nobody, unless he has tried himself to unify such a huge compilation, can be less than respectful to the result; but the new volume somehow contains rather less of direct interest to medical readers than might perhaps have been expected. This is probably as it should be. The editor of a comparative work has to resist attempts to turn it into a clinical or a veterinary textbook. The veterinarian is very well served, as might be expected. There is a great deal for the fertility expert, even in the solidly zoological sections: on the other hand two sides and three lines seem a meagre allotment for contraception: the mechanics of human coition and its associated physiology, which have been remarkably little studied compared with that of economically important animals, deserved proper treatment (it is a little disconcerting to be referred to Dickinson's book and to "pornography" for information on this clinically not unimportant matter, while other papers remain unquoted). Another virtual defaulter is the physiology of orgasm in man and lower animals, which seems to belong here. More serious is the perpetuation of the idea that a recent suppositious case of human parthenogenesis "could not be disproved" by reciprocal grafts. In a work of this size these are very minor faults which may reflect the fact that Prof. A. Walton unhappily died before he was able to revise the sections he contributed.

The visual material is magnificent: much of it is familiar to a few biologists, but for the doctor and the biologist not working in this field, processes which he knows but has never seen, such as the formation of the pronuclei and the submicroscopic structure of sperms, are made brilliantly actual—indeed the vast range and refinement of available biological techniques is one of the main lessons to be learned from the book. It should be borrowed for this alone (at the price, individual buyers will be few).

## The Adrenal Circulation

R. G. HARRISON, D.M., Derby professor of anatomy, University of Liverpool; M. J. HOEY, B.SC., demonstrator, department of anatomy, University of Liverpool. Oxford: Blackwell Scientific Publications. 1960. Pp. 77. 25*s*.

THERE is increasing evidence that the neurovascular system of the adrenal cortex influences the release of adrenocortical hormones from the gland. Professor Harrison's studies of adrenal vasculature are well known, and with the cooperation of Mr. Hoey he has now collected his observations into this small book.

In the first section, the results of investigations of the anatomy of the adrenal blood-vessels in laboratory animals (rats, rabbits, cats, dogs, and macaque monkeys) by microarteriographic and injection techniques are reported. The adrenal arteries form a subcapsular plexus which gives rise to two types of vessels: (1) a capillary network, which forms sinusoids around the cortical cells and finally drains into the medulla; and (2) the arteriæ medullæ, small straight arteries without branches which run directly through the cortex to reach the medulla. The arteries of the adrenal are end-arteries to the zona fasciculata of the cortex, and after their ligation focal lesions are seen in this zone. The venous drainage is mainly through a large trunk arising from the hilum of the gland, but small veins leave the gland at its periphery in com-

pany with the arteries. Unfortunately the authors have not extended their investigations to man, though the description, by others, of similar venæ comites of the human adrenal arteries indicates that when a subtotal adrenalectomy is performed the main adrenal vein need not be preserved.

The second section of the book describes microradiographic studies of the effect of various substances on the distribution of blood to the adrenal cortex of animals, from which the authors conclude that the catecholamines, adrenochrome, and corticotrophin cause cortical hyperæmia, probably by constricting the arteriæ medullæ. The rather detailed presentation of the experimental data obscures the evidence for the authors' conclusions, while the variable and at times unphysiological body-weight doses and time-intervals may be found confusing. The finding that a similar redistribution of blood-supply follows injection of 0·2 ml. saline intramuscularly in anæsthetised rats makes it difficult to separate the influences of specific and non-specific factors. In the absence of studies of blood-flow and the secretion of steroid, the extent to which the degree of vascularisation can be taken as an index of adrenal function is doubtful. Similar study with more refined techniques is clearly indicated.

Though this book will appeal mainly to those directly concerned with its rather limited scope, we hope its appearance will stimulate interest in this new and important branch of adrenal physiology.

### Sea Surgeon

JAMES S. HALL, O.B.E., M.B., F.R.C.S.E. London: William Kimber. 1960. Pp. 205. 25*s*.

THE years 1939 to 1945 brought novel experiences to many doctors, and the strangest adventures did not always befall those who served farthest afield. But few who remained at home can have had such an unusual war as Dr. Hall. Within a fortnight of the outbreak, his quiet general practice near Deal suddenly changed, and he found himself adopted as medical officer by the scores of ships on passage, under Naval control, through the Downs.

He admits his maritime knowledge was negligible, and he had no particular wish to improve it. Yet he undertook to answer a succession of emergency calls from over 40 square miles of sea lying between his home, Walmer, and the notorious Goodwin Sands. Not all the difficulties were professional ones, and he tells how he had to master the International Code, organise his own reporting system, and provide his own ferry service. In the first twelve months, he visited some 300 ships lying in the Downs. Then the fire of cross-Channel guns made the anchorage untenable, and the need for his services ceased, only to recur more acutely in the period after D-Day.

Some of the technical aspects of his work have already been described in our columns,[1] and this account is for popular reading. There is little reference in it to the dangers involved or to the demands such an arduous job made, particularly in winter, on a man who combined it with his ordinary practice ashore. But his colleagues who read it, and who later have to answer a night call, may console themselves with the thought that there are worse tasks than driving a heated car along a smooth road to examine a patient in a bed which stays on an even keel.

### Lupus Vulgaris Cutis in Denmark 1895-1954

OLE HORWITZ, M.D., research physician, dermatological department, Finsen Institute, Copenhagen. Translated from the Danish by HARRY COWAN, B.SC. Copenhagen: Finsen Institute, 1960. Pp. 250. $6·50.

WITH the steady decline in morbidity of all forms of tuberculosis in Great Britain during the past fifteen years, and the comparative rarity of new cases of lupus vulgaris, this work should be salutary. Many readers will be surprised to learn that Dr. Horwitz, basing his deductions on the incidence of lupus in Denmark, estimates that there are about 1 million sufferers from active lupus vulgaris in the world, with an annual incidence of 50,000 fresh cases.

1. *Lancet*, 1959, i, 1268.

He has made a close study of 3902 cases (1140 males and 2762 females) admitted to the Finsen Institute between 1895 and 1954. They form about 80% of the cases diagnosed in Denmark. The incidence, which at the turn of the century was 25 males and 71 females per million, had fallen to 2 and 4 respectively at the end of the period. In England, lupus is now complicated by other forms of tuberculosis in only some 10–15% of cases, but Horwitz reports 70% amongst his series. The age patterns of lupus and pulmonary tuberculosis resembled each other, with a rather sharp peak at the age of 20 and a more rounded one at 50. Typing of tubercle bacilli was performed in 214 of the patients and the majority of organisms were human. Of those patients found to have more than one type of tuberculosis, lupus was recorded as the first tuberculous disease in 38%; it appeared simultaneously with another form in 19%, and developed after another tuberculous disease in 43%.

Horwitz tried to correlate the incidence of lupus with the patient's occupation and social position, but the information available led to no certain conclusions. The distribution of patients according to occupation mainly corresponded with that of the general population. Of the 1391 deaths amongst the lupus patients admitted, in 39% of the males and 31% of the females death was attributed to tuberculosis, the proportion being higher among children and young persons.

This book, which ends with a long appendix containing an array of statistical information, should be very valuable not only to those interested in lupus but also to workers contemplating a similar large investigation of other diseases.

**Varicose Veins** (3rd ed. Bristol: John Wright. 1960. Pp. 356. 63*s*.).—The new edition of this well-liked manual has been completely rearranged and largely rewritten, and the result is a very satisfactory achievement for the author, Mr. R. Rowden Foote, and his assistant, Mr. A. Gordon Dingley. The illustrations have been brought up to date and many new coloured pictures and useful line diagrams are included, illustrating advantages and disadvantages of good and bad practice. The pros and cons of various methods of investigation and management of varicose veins, complicated and uncomplicated, and of the post-thrombotic syndrome are carefully set out and discussed. The author is now clearly in favour of surgical extirpation but rather critical of the use of sclerosants. The new edition ensures the book a continuing place in the literature of this troublesome and common condition.

**Chromatographic and Electrophoretic Techniques** (2nd ed. London: Heinemann Medical Books. 1960. Vol. 1, Pp. 617. 65*s*. Vol. 2, Pp. 215. 30*s*.).—When Dr. Ivor Smith and his colleagues produced their book on chromatographic techniques in 1958 it was widely welcomed. This second edition still carries the great advantage of the first, by referring all techniques to a single apparatus. It contains new chapters on the chromatography of radioactive compounds and on ion-exchange celluloses. A second volume deals with electrophoretic techniques; and particularly useful will be the contribution by J. Kohn on his cellulose-acetate electrophoresis and on the application of his technique to immuno-electrophoresis. Other chapters are by J. Bodman on agar gel, starch block, starch gel, and sponge-rubber electrophoresis, and by Jacqueline Weiss on hæmoglobins.

**A Glimpse of Arcadia** (London: Michael Joseph. 1960. Pp. 204. 13*s*. 6*d*.).—Neither Karl Marx nor Charles Mayhew found much cause for merriment in the condition of the labouring poor of London in 1860. From the same material Mr. Macdonald Hastings has written an entertaining little story about the mudlarks, the finders, and the last of the Thames salmon-fishers. The ending is just too happy to be true. The main interest for us was in an admirable picture of Weil's disease acquired in the sewers and a fervent plea for a cleaner Thames, which we echo most heartily.

THE LANCET

LONDON 21 JANUARY 1961

## Health Centres or Medical Centres?

HEALTH centres were to transform general practice; and, though it was ANEURIN BEVAN that called them "a key feature of the new health service",[1] they were a medical rather than a political invention. The Medical Planning Commission in 1942 wanted groups of practitioners to work from "a single centre at which all of them would see their own patients and share equipment and the services of secretarial, domestic, and dispensing staff. "The health centre", the Commission said, "must on the one hand preserve the professional independence of the cooperating general practitioners" but on the other hand must "be capable of becoming an organised unit in an integrated medical service".[2] Under the National Health Service Act the clinics of the local authority were to be brought into relation with general practice by having them under the same roof, so that the techniques of curative, preventive, and what we tentatively called "functional" medicine—the pursuit of positive health—might be used side by side.

From the high hopes and detailed plans of our series of articles, in 1947, on the Health Centres of Tomorrow,[3] it is depressing to come down to the facts of today as set out in Dr. J. SLUGLETT's report to the Medical Practitioners' Union.[4] Only 14 centres such as were proposed in the Act have so far been opened in Great Britain; only 136 out of 23,000 general practitioners work in them; and only 33 of these practise exclusively in the centre. Why have health centres been so unpopular? Why, for example, were only 4 out of 150 of the 250 doctors in Leeds in favour of participating in a new one? Some of the answers are evident from Dr. SLUGLETT's report, which has the merit of also covering other forms of health centre—7 group-practice centres, 2 diagnostic ones, and 2 general-practice teaching units.

The idea of providing ancillaries for the family doctor, and having local-authority services in the same building, was excellent in theory: and the plan had obvious attractions for practitioners, since they could do their clinical work better, and would have more time for it, more leisure, and a home life separated from their practices. But doctors on the whole lacked the confidence in local authorities needed for easy cooperation, and in many places the authorities' approach to the new scheme did nothing to make cooperation easier. Often, though the local medical committee was consulted, the opinion of the practitioners of the area was not ascertained before a decision was made. Sites for centres were not always suitable, and on new estates the centre was often the last building to be erected—by which time the residents were already on the lists of neighbouring practitioners. Though all practitioners were invited to apply, at only one centre have there been more applicants than vacancies (7 doctors applying for 6 places): at all the others there were too few. Even the Manchester University teaching centre attracted only 3 of the practitioners in the neighbourhood, though a 4th joined later. (Dr. SLUGLETT does not mention that in at least one area the centre has remained ostracised by all the local doctors.) The fact that, even now, of the practitioners actually working in a centre, very few confine their activities to it, is attributable to fear that rents may be raised or some other obstacle may arise, obliging the doctors to leave. So far this has not happened; and those prophets who thought that local authorities would try to control or regiment the practitioners, or interfere with their work, have been likewise wrong. But on the other and positive side, only two authorities allow the general practitioners to undertake their clinics in the centre—though in this decision some of them have been influenced by the local medical committee.

Has the service benefited from the experiment? The doctors have benefited in that they have had congenial surroundings, professional contact, and (where they have moved entirely into the centre) privacy at home—though the majority have in fact had to bear the cost of two establishments. Have the patients benefited? In general, probably they have; though a former report on three years in a centre suggested that the majority still preferred the domestic surgery to the more institutional one. Arrangements by which all the facilities likely to be needed for diagnosis were to be at hand were attractive; but, unless a centre can provide pathological, radiological, and cardiac services, continouusly, the patient may have to be given another appointment; and this defeats the original object, since a similar investigation could be had in a neighbouring hospital, plus a specialist's opinion. Have outside doctors lost? That they might do so seemed not improbable in view of the considerable concealed subsidy the participants were receiving; but there seems to be no evidence that the centre practitioners have increased their lists at the expense of others. What of the cooperation with the local health authority? Bristol and Manchester say that it is excellent; and the authorities have been scrupulously fair towards the practitioners who have chosen to work in the centres—except perhaps as regards the clinics. Finally, have the hospitals benefited? Manchester says that, compared with corresponding practices outside, practices in the health centre refer one-third fewer patients to hospital, and the estimated saving of this to the Exchequer is £12,000 a year. As such estimates are apt to be disputable, and in Manchester the costs of the teaching unit have to be considered, figures from other centres would be interesting. One of the major arguments against having more centres is that they are expensive: to provide 22,000 practitioners with such accommodation as they have in the unofficial centres at Harlow would, it is said, entail capital expenditure of some £170 million, with larger maintenance

1. See *Lancet*, 1948, i, 656.
2. *Brit. med. J.* 1942, i, 743.
3. *Lancet*, 1947, i, 32 et seq.
4. Medical Practitioners' Union: Health Centres Report. Presented to the annual meeting of the Union on Oct. 22, 1960. Obtainable from the Union at 56, Russell Square, London, W.C.1.

costs thereafter. But such expenditure would not necessarily be wasteful if the strain on the hospitals were greatly lessened.

One reason why the hopes of 1947 have not been fulfilled is, as Dr. SLUGLETT shows, that doctors and local authorities have often been at cross-purposes. But there could be a more fundamental reason—namely, that the health centre, for all its attractions, does not really fit into the framework of medical care in a country such as ours. Some saw the centre as a group in which the doctors, closely cooperating, would specialise in function, and the patients would become patients less of the individual than of the group. But in this country, where specialist care can usually be got at a hospital within reasonable distance, we seldom need groups of this kind—" composite general practitioners " as they have been called. A different and more realistic view of the centre was as the workplace of a collection of practitioners practising personal care; but, if FOX [6] is right, a largish centre with local-authority activities is not really a very good headquarters for a doctor undertaking personal care; and to have more than three practitioners in partnership promotes too much organisation and too little sense of personal relationship. It is noteworthy that the Bristol health department, where so much was done to create and test different kinds of centre, also brought forth one of the first papers questioning whether, after all, it may not be better for family doctors to practise from their homes.[7] Nevertheless, the Manchester school produced last year some telling arguments in favour of preserving health centres in our schemes for the future.[8] Nowhere but in a centre (it was suggested) is there a chance of doctors learning to practise, and actually practising, the new kind of medicine in which full attention is paid to social factors, the personal services now given by local authorities are developed, and full use is made of members of allied professions.

The council of the Medical Practitioners' Union, which invited Dr. SLUGLETT to report, appends some important comments of its own. After pointing to the apathy alike of the Ministry of Health, the local authorities, and our profession, as regards health centres, it says firmly that " some new unit of general practice is required ", and also that strong inducements will be needed to overcome the vested interest of most practitioners in maintaining the status quo.

" The plan to unify the preventive and curative services in one building, and to associate them closely with the hospital service is basically sound. Sound, and indeed essential to the vitality of general practice . . . The isolated practitioner who strives to provide a good service without secretarial and nursing help and out of contact with the health and welfare service, is fighting a losing battle."

This being so, the council says, both Ministry and profession ought to develop a new and positive approach. But, pending such a fresh initiative towards making health centres work, the council points out that some of their benefits could be provided by partnerships to which local authorities were willing to attach their health visitors and nurses. It would like to see more and better experiments in health centres initiated by the Ministry, in conjunction with the profession, " through the agency of selected local authorities "; but, until we have results from these, it would favour the construction of " group practice premises (they might be called Medical Centres) " financed out of a trust fund established by the Ministry of Health. Practice in these publicly owned centres, with their advantages both to doctors and to patients, would be offered to local doctors at low cost (though with certain stipulations which would make for serious whole-time work from the centres, sometimes including teaching); and local authorities would be far more likely to attach their staff and their clinics to such centres than to privately owned practices.

6. Fox, T. F. *Lancet*, 1960, i, 743.
7. Wofinden, R. C., Parry, R. H. *ibid.* 1952, i, 1297.
8. Susser, M. *ibid.* 1960, i, 983.

## Monoamine-oxidase Inhibitors in Treatment of Angina Pectoris

ASSESSMENT of new remedies is exceptionally difficult in angina pectoris. The reasons for this include the spontaneous fluctuations in the frequency and severity of attacks, the influence of weather and of emotional factors, and the fact that sometimes improvement takes place whatever the treatment. EVANS and HOYLE [1] actually obtained better results with a placebo than with supposedly effective preparations, and COLE et al.[2] showed that more than 50% of patients were likely to improve steadily for some weeks as a result of the extra care received during a clinical trial—an effect which they termed the ski-slope response. New methods of treatment should as far as possible be tested in carefully controlled trials; and the double-blind method is usually recommended in angina pectoris, to guard against bias on the part of the physician in assessing the results. KATZ [3] believes that, besides the usual conditions for such a trial—use of tablets identical in appearance, randomisation of the order in which the preparations are given, and statistical analysis of results—the trial substances should be administered to the patient in at least two separate sequences. Even if these conditions are fulfilled difficulties remain: the numbers required are relatively large since some patients will evince the ski-slope response, and the assessment of improvement is not easy. Objective criteria, such as the Master two-step test, are unsatisfactory for this purpose, and a record of the number of anginal attacks is by itself unreliable—a patient's activities may vary from week to week, or his exercise tolerance may have improved even though the frequency of attacks remains unchanged. Recording the amount of trinitrin used is open to a similar objection. A possible weakness of the double-blind trial is that the dose is usually predetermined and is not varied, but there seems to be no good reason why this defect should not be overcome by altering the dose of both test and control tablets according to the individual patient's response. A double-blind trial is highly artificial in as much as no patient receives a drug without expecting

1. Evans, W., Hoyle, C. *Quart. J. Med.* 1933, **2**, 311.
2. Cole, S. L., Kaye, H., Griffith, G. C. *Circulation*, 1957, **15**, 405.
3. Katz, L. N. *Ann. N.Y. Acad. Sci.* 1956, **64**, 505.

some benefit, and this may affect his response to the control tablet. The advantage of the double-blind trial lies in the revelation of just how much improvement is attributable to emotional causes.

The monamine-oxidase inhibitor group of drugs have been closely studied since CESARMAN [4] observed in 1957 that angina pectoris was strikingly improved in some psychiatric patients receiving iproniazid. Other favourable reports soon followed,[5–7] but these trials were uncontrolled. Subsequent double-blind trials [8–10] in this country failed to confirm these encouraging results, but SHOSHKES et al.[11] in the U.S.A. reported significant improvement. With iproniazid there is a considerable risk of toxic reactions—notably liver damage—and other monoamine-oxidase inhibitors have been developed in an attempt to overcome this serious drawback. MACKINNON et al.[12] reported significant improvement in 41% of patients who received pheniprazine hydrochloride (' Cavodil ') in a double-blind trial. On p. 139 of our present issue Dr. MURPHY and his colleagues describe a restricted sequential trial of 1-benzyl-2-pivaloyl-hydrazine (' Tersavid '). They found that in a dosage of 100 mg. four times daily this drug relieved angina pectoris no better than a placebo. This result is especially interesting since in 1959 at a congress in Lugano [13] Dr. MURPHY and Dr. BARBER reported significant improvement in nearly two-thirds of a group of patients receiving the same preparation in an uncontrolled trial; and at the same meeting many other reports [14] (all except one of which were uncontrolled) suggested that tersavid was effective against angina pectoris. In a double-blind trial, however, PHEAR and WALKER [15] could detect no significant effect. Dr. ALLANBY and his colleagues report on p. 138 their results in a controlled trial of nialamide (N-[2-benzylcarbamoylethyl]-N′-isonicotinoylhydrazine). Unfortunately the numbers were too small to yield a statistically significant result, but they conclude that nialamide may perhaps benefit one in four patients with angina; and they remark that, had the trial not been controlled, about 60% of the patients would apparently have improved. The effect of the ski-slope response should be remembered in assessing the conclusions of the Lugano conference on tersavid in which it was stated that 384 (65%) of 594 patients responded; the majority of these patients were participating in uncontrolled trials.

At present, therefore, there are no grounds for believing that monoamine-oxidase inhibitors represent an important advance in the treatment of angina pectoris. There seems to be good reason for ensuring that all new remedies for angina pectoris are submitted to carefully controlled trials at the outset: this would surely save much trouble and disappointment.

4. Cesarman, T. *Arch. Inst. Cardiol. Mex.* 1957, **27**, 563.
5. Cossio, P. *Amer. Heart J.* 1958. **56**, 113.
6. Master, A. M. *ibid.* p. 570.
7. Towers, M. K., Wood, P. *Brit. med. J.* 1958, ii, 1067.
8. Dewar, H. A., Horter, A. R., Newell, D. V. *Brit. Heart J.* 1959, **21**, 315.
9. Snow, P. J. D., Anderson, D. E. *ibid.* p. 323.
10. Fife, R., Howitt, G., Stevenson, J. *Brit. med. J.* 1960, i, 692.
11. Shoshkes, M., Rothfield, E. L., Becker, M. C., Finkelstein, A., Smith, C. C., Wachtel, F. W. *Circulation*, 1959, **20**, 17.
12. Mackinnon, J., Anderson, D. E., Howitt, G. *Brit. med. J.* 1960, i, 243.
13. Murphy, F. M., Barber, J. M. *Cardiologia*, 1960, **37**, suppl. 2.
14. *ibid.*
15. Phear, D., Walker, W. C. *Brit. med. J.* 1960, ii, 995.

## Hypogammaglobulinæmia

SOME two years ago we drew attention to a group of diseases characterised by the finding of agammaglobulinæmia.[1] The use of more sensitive techniques has shown that probably γ-globulin is never completely absent from the serum, and a more accurate (if unwieldy) name is " hypogammaglobulinæmia ". It has become obvious that this is no very rare condition, and undoubtedly some cases still remain undiagnosed owing to insufficient awareness of its existence. Yet, since effective treatment is now feasible, a high standard of diagnosis is much to be desired.

Hypogammaglobulinæmia is not a single disease entity. No entirely satisfactory classification is yet possible; but attempts have been made by several workers.[2 3]

*Congenital hypogammaglobulinæmia* refers to cases in which manifestations of immunological inadequacy appear shortly after birth. Most of these cases have been familial and in males.[3–5] A sex-linked mode of inheritance has been suggested; but a few cases have been reported in girls.[6–8] These may represent a different mode of inheritance; but in some the disease may, in fact, have been acquired at an early age.[9]

In *primary acquired hypogammaglobulinæmia* the disease, for which no underlying cause can be discovered, first appears after early childhood, and it is as common in females as in males. The deficiency seems often to be less nearly complete than in the congenital cases.

*Secondary acquired hypogammaglobulinæmia* is found in some cases of multiple myeloma, lymphoma, and chronic lymphatic leukæmia [2 5] in which synthesis of γ-globulin has failed. This category does not include diseases such as nephrosis, hepatic failure, and the familial dysproteinæmia of HOMBURGER in which hypogammaglobulinæmia is not an isolated defect.[2]

Clinical interest centres mainly in the congenital and primary acquired forms. The commonest clinical manifestation is repeated severe bacterial infections—for example, pneumonia, otitis media, sinusitis, furunculosis, or pyogenic meningitis. Other patients have chronic bronchiectasis which progresses inexorably despite orthodox medical or surgical treatment. The first reported cases of the congenital disease were described in this country by HUTCHISON.[10] The patients were two brothers who died of pneumonia caused by a protozoon, *Pneumocystis carinii*. This organism has been detected in several subsequent cases,[11 12] so susceptibility to infection is not confined to bacteria. On the other hand, there is evidence that hypogammaglobulinæmia does not impair the response

1. *Lancet*, 1958, i, 1317.
2. Firkin, B. G., Blackburn, C. R. B. *Quart. J. Med.* 1958, **27**, 187.
3. Gitlin, D., Gross, A. M., Janeway, C. A. *New Engl. J. Med.* 1959, **260**, 72.
4. Bruton, O. C. *Pediatrics*, 1952, **9**, 722.
5. Good, R. A., Zak, S. J. *ibid.* 1956, **18**, 109.
6. Arnaud-Battandier, R., Cabannes, R., Legendre, E., Sarfaty, R. *Pédiatrie*, 1955, **10**, 880.
7. Delaitre, R., Fonty, P. *Bull. Soc. méd Hôp. Paris*, 1955, **71**, 239.
8. Pearce, K. M., Perinpanayagam, M. S. *Arch. Dis. Childh.* 1957, **32**, 422.
9. Mollison, A. W., Brackenridge, R. G., MacLeod, M. *Scot. med. J.* 1960, **5**, 448.
10. Hutchison, J. H. *Lancet*, 1955, ii, 844, 1196.
11. Bird, T., Thomson, J. *ibid.* 1957, i, 59.
12. McKay, E., Richardson, J. *ibid.* 1959, ii, 713.

to tuberculous infection.[13 14] Diarrhœa or steatorrhœa is common in both congenital and acquired cases.[10 15 16] Occasionally the patient presents with a syndrome closely simulating rheumatoid arthritis.[17] Most patients with either congenital or acquired hypogammaglobulinæmia seem to respond normally to the common virus infections such as measles, rubella, chickenpox, mumps, and the upper respiratory infections; but there have been a few reports of vaccinia gangrenosa causing death in young infants.[18–20] GITLIN [21] has suggested that such cases fall into a separate category—namely, the transient hypogammaglobulinæmia of infancy. Normally, in the early weeks of life maternal γ-globulin is gradually lost from the infant's circulation, and γ-globulin synthesis by the infant does not make good this loss. In some this "physiological" hypogammaglobulinæmia may be excessive.

The diagnosis must be confirmed by the demonstration of a very low serum level of γ-globulin. The Medical Research Council working party on hypogammaglobulinæmia requires the level to be below 200 mg. per 100 ml. after the age of 6 months for inclusion of a case in their clinical trial. Several methods may be used to measure the γ-globulin fraction of the serum. A simple screening technique, applicable in most laboratories, is Kunkel's zinc-sulphate turbidity test.[22] While usually employed to show an increase in the serum-γ-globulin in liver disease, it can equally be used to demonstrate a decrease. A positive zinc-sulphate turbidity test excludes hypogammaglobulinæmia. Free-boundary or paper electrophoresis techniques are somewhat laborious but are more specific and should always be performed in these cases. The most accurate quantitative method for estimating the serum-γ-globulin is precipitin diffusion through a gel.[23] This test is not available in many laboratories, but it can be arranged in suitable cases through the M.R.C. working party. Every case should be investigated as fully as possible, and there are several methods of demonstrating the severe immunological inadequacy of hypogammaglobulinæmic patients. Such tests show very low or absent titres of isoagglutinins against heterologous blood-group substances; the antistreptolysin-O titre is also negligible. The Schick test is usually positive despite previous inoculation against diphtheria. Injections of other potent bacterial antigens, such as pertussis and T.A.B. vaccines or tetanus toxoid, fail to stimulate antibody formation. Although these patients seem to cope successfully with virus infections, antibodies against the infecting viruses are not found in the serum.[5] The same lack of antibody production has been demonstrated after apparently successful vaccination against smallpox,[10] and after inoculation with vaccines prepared against influenza, mumps, and poliomyelitis.[5] It is not yet understood why the inability to produce antibodies towards virus antigens should be associated with normal clinical responses to the virus infections. Finally, homografts of skin from normal donors are not rejected in the normal way by hypogammaglobulinæmic patients. Some grafts have survived permanently [5]; others have been replaced by fibrous tissue at a much slower rate than in the normal recipient.[9]

Children and adults with hypogammaglobulinæmia can be protected from severe bacterial infections by long-continued ingestion of broad-spectrum antibiotics. There are, however, obvious dangers in this prophylactic measure, which moreover fails to protect against infection by *Pneumocystis carinii*. A preferable treatment is the weekly intramuscular administration of pooled γ-globulin in a dosage of 0·025 g. per kg. body-weight. γ-globulin may be had for proved cases in this country from the M.R.C. working party.

13. Elphinstone, R. H., Wickes, I. G., Anderson, A. B. *Brit. med. J.* 1956, ii, 336.
14. Parkes, R. *ibid.* 1958, i, 973.
15. Cook, I. A., Melrose, A. G. *Scot. med. J.* 1958, **3**, 135.
16. Cooke, W. I., Weiner, W., Shinton, N. K. *Brit. med. J.* 1957, i, 1151.
17. Good, R. A., Rotstein, J., Mazzitello, W. F. *J. Lab. clin. Med.* 1957, **49**, 343.
18. Keidan, S. E., McCarthy, K., Haworth, J. C. *Arch. Dis. Childh.* 1953, **28**, 110.
19. Kozinn, P. J., Sigel, M. M., Gorrie, R. *Pediatrics*, 1955, **16**, 600.
20. Somers, K. *Arch. Dis. Childh.* 1957, **32**, 220.
21. Gitlin, D. *in* Year Book of Pediatrics, 1955–1956. Chicago.
22. Discombe, G. *Lancet*, 1959, i, 619.
23. Gell, P. G. H. *J. clin. Path.* 1955, **8**, 269.

## Annotations

### CENTRAL STERILE SUPPLY

MOST sterilisation procedures, apart from those for unwrapped instruments to be used in operating-theatres, should be centralised.[1 2] A well-organised central sterile supply department (C.S.S.D.) saves nurses' time, and thus enables ward dressings to be done with quiet efficiency instead of amid the rush and clatter involved in sterilising, or purporting to sterilise, the bowls, instruments, and syringes just before and even during the dressing round. C.S.S.D.S also offer the prospect of economical use and better supervision of expensive sterilising apparatus. Really efficient supervision is necessary because the individual pieces of modern sterilising apparatus generally cost about three times the price of the old, and need to be properly maintained if they are to give the reliable sterilisation which has hitherto been lacking in a great many places, and if they are to maintain the high rate of output which makes their use really economical. So far, there has been only limited experience of C.S.S.D.S in Great Britain; and it was a useful enterprise therefore to gather into an informal "club" a great proportion of those who are working at or closely concerned with the problems. Last March the club held its first meeting, at Portsmouth; and on Dec. 19 and 20, at Cambridge, the second meeting brought together a gathering of some 50 people. Most of the doctors were bacteriologists or clinical pathologists, and most of the others present were nurses either in charge of or associated with C.S.S.D.S. Happily there were also a few surgeons and administrators and one pharmacist.

During a busy two days the members of the club closely examined the new Nuffield experimental C.S.S.D. at Addenbrooke's Hospital and discovered at first hand that the nursing staff of the hospital were reacting favourably to this innovation, which was being very gradually introduced. In general, the meeting was convinced by Brigadier J. D. Welch, who described the Nuffield unit in detail, that C.S.S.D.S were not merely possible but essential. American experience and methods so far used, he sug-

1. *Lancet*, 1960, ii, 353.
2. *ibid.* p. 639.

gested, might set a pattern of extravagant use of labour which we should not wish to follow in this country. In the U.S.A. the number of C.S.S.D. staff per 100 beds served ranged from 4 to 14, whereas at Addenbrooke's they hoped eventually to manage with something like 1·5 orderlies per 100 beds served. These calculations, as clearly emerged, are necessarily tentative at this stage; but undoubtedly the potential output of a well-organised C.S.S.D. is much greater than has been generally appreciated. It is most important that administrators should convince their financial masters that each new C.S.S.D. is to some extent an experiment: it will be time enough in another five years or so to consider what is the modal form of establishment.

Meanwhile, at Cambridge, Dr. E. M. Darmady of Portsmouth, president of the club, and Brigadier Welch debated the relative merits of the Portsmouth one-for-one exchange system, which uses panniers for transporting the sterile goods, and the Addenbrooke shopping-list scheme, by which a ticked-off list of ward requirements is received in the C.S.S.D. each morning and a delivery round is then made to satisfy the indicated needs. Other discussions centred on the place of disposable syringes; methods of handling and transporting contaminated articles; means of storing sterile and non-sterile goods; the safest and most efficient wrappings for packs; and the economics of the contribution that might be made by industry, especially in the form of various disposable instruments and hollow tubes sterilised by radiation and cheap enough to be discarded after being used only once. Sterilisation of water for operating-theatres was discussed, as was also the possibility of disinfecting woollen blankets and certain other articles by steam of subatmospheric pressure giving temperatures of 60–90°C.

To relieve the discussion of much that was essentially technological, although vitally important, there was a lively session on responsibility. This is a matter of fundamental importance. It was agreed without dissent that each C.S.S.D. must have a member of the medical staff who answered to his colleagues for the reliability and up-to-dateness of the methods employed in the C.S.S.D. and the competence of the person in day-to-day charge. Such a doctor might be anyone with real interest in the prevention of hospital infection. He might be a bacteriologist, a surgeon, a physician, a member of the staff of the medical officer of health—all that mattered was that he was interested and was a full member of the control-of-infection committee, through which his advice could be given and the opinions of his medical colleagues made known to him. Who should be in charge of the day-to-day work? The solitary pharmacist firmly stated the case for having a pharmacist in charge. Many thought that a nurse was required; but others believed that this was not the proper use of a trained nurse's skill. Nurses are needed in C.S.S.D.s, the argument went, at this stage during which the variability of ward requirements needs to be sympathetically assessed; but when all those novel problems have been experienced and solved, any intelligent person with organising power—a man or woman with executive experience of a wholesale-retail trade relationship, for example—could ensure that wards have always on hand all that they need in the way of sterilised equipment and materials. What is clear is that this post will be properly filled only by someone with a high sense of responsibility, drive, and intelligence, and the right personality. Whether the right person at present is most likely to be a nurse (male or female), a pharmacist, or a laboratory technician the club wisely did not try to say; but it was pretty clear that the salary-scale, at present values, should not be less than £1000–1200 a year. Any lower salary would be unlikely to attract a person of sufficient training and capacity. In this connection the dangers inherent in the use of the word "supervisor" were stressed. In the N.H.S. the word apparently denotes a grade below what the club regarded as essential. Charge-hands, also, would need to be well selected and given the appropriate charge-hand responsibility pay, because too often in the past we have seen bad results from leaving autoclaves under the care of porters—and not porters of the highest grade at that.

To compensate for all this, those who have to find the money will surely be comforted to know that it is estimated that two modern high-vacuum, high-pressure autoclaves, each of about 15 c. ft. capacity, could easily serve 1000 beds. With a third autoclave as a stand-by, and under regular engineering checks and maintenance, there is every reason to say confidently that economic use of plant and time will be combined with a guarantee of sterility such as has hitherto not been provided for doctors and patients.

## BRONCHITIS AND THE MINISTRY OF LABOUR

IN this country bronchitis causes more unemployment than any other illness. The Ministry of Pensions and National Insurance reports that during 1956–57 10% of all men unemployed for more than three months owing to illness were suffering from this disease.[1] In spite of this, the Ministry of Labour appears unaware that bronchitis is a major cause of unemployment. Its Report on Disabled Persons for 1959 [2] makes no reference to this disease. How this state of affairs has come about is discussed by Caplin and Silver [3] in their study of bronchitis and unemployment in East London.

These workers point out that, of 49,000 persons in England and Wales registered with the Ministry of Labour as disabled by bronchitis or bronchiectasis, only 8% were recorded as unemployed. But this low proportion does not reflect the true position. If a man, whether registered as disabled or not, is signed off work by his family doctor because of illness, he is not recorded by the Ministry of Labour as unemployed; and the number of men registered with the Ministry of Labour as disabled by bronchitis is probably a small proportion of the number of men losing time from work because of the disease. Caplin and Silver found that only 17% of the 83 men with moderately severe bronchitis whom they interviewed were registered as disabled. The responsibility of registering a man as disabled by bronchitis rests with his physician, his employer, or himself. Since there are few suitable jobs for patients with bronchitis, registration is often regarded as a waste of time by both physician and patient. Since the physician is likely to pass his patient as fit for work only if he knows that there is work fit for his patient, many men out of work owing to bronchitis continue to receive sickness benefit (and National Assistance) though they could work if suitable work were available.

As Caplin and Silver show, a high proportion of bronchitics lack a skill (46% of their subjects) and are over the age of 55 (65% of their subjects). Because of their

1. Ministry of Pensions and National Insurance: Digest of Statistics Analysing Certificates of Incapacity, 1956–57; table IX.
2. Ministry of Labour: Report on Resettlement of Disabled Persons, 1959. H.M. Stationery Office, 1960.
3. Caplin, M., Silver, C. P. *Brit. J. Dis. Chest.* 1960, **54**, 297.

disability bronchitics require light sedentary work in a clean dry atmosphere and an easy journey from home; and they must be able to earn a wage that exceeds their sickness benefit and National Assistance. For the disablement resettlement officers to find work for such men is a formidable and, all too often, an impossible task. Such suitable jobs as exist are usually in large well-organised industries which reserve them for their own employees.

This hidden unemployment problem could be solved by the provision of local sheltered workshops in which breathless patients could work in comfort under medical supervision, in order to ensure that each patient had the best chance of making an economic contribution and that patients too ill for work were discharged. Properly planned and supervised workshops taking advantage of voluntary help need not necessarily run at a prohibitive financial loss. The design and planning of such workshops, preferably integrated with local industry, is a challenge to our industrial society. Many of the men in need are those who have done the heaviest and dirtiest jobs: they should have the opportunity of keeping their economic self-respect when increasing breathlessness robs them of their ability to labour.

Meanwhile, physicians should be ready to recommend men for registration as disabled, and to recommend that they be found light or, where necessary, sheltered employment. If suitable employment in the earlier stages of the disease delays its progress, then early registration might become an important preventive measure. Unemployment due to bronchitis is a national problem. The blurring of the distinction between " sickness " and " unemployment " should no longer be allowed to impede its solution.

## ROBUST AND HEALTHY?

THE spirit of the new report [1] of the chief medical officer to the Ministry of Education lies in the words " Britain's children robust and healthy ". There can be no doubt that the improvement in the health of British schoolchildren since the School Health Service started in 1907 has been immense. During its first fifty years, undernourishment ceased to be an important cause of ill health. Deaths per 1000 living fell from 3·6 to 0·4 in the 5–10-year-olds and from 2·1 to 0·37 at 10–15.[2] During 1958 and 1959, only about 5% of schoolchildren contracted a notifiable infectious disease. Poliomyelitis reached its lowest level for 13 years, and vaccination against it was undertaken vigorously. Tuberculosis continued to decline, and the reduction was most striking among children of school age. By 1959, 99% of the milk drunk by children in school was pasteurised. 1959 was the first year in which there was no death from diphtheria. " We ought not to forget ", Sir John Charles remarks, " that as recently as 20 years ago, 55,000 persons contracted diphtheria annually, of whom almost 3,000 died." But its incidence among schoolchildren has recently increased, and the report was published during a disturbing outbreak of diphtheria in Camberwell.

Fifty years from now the schoolchild's condition and the dangers to his health today may seem as appalling as those of 1910 do now. Something will, we hope, have been done about accidents, which now kill more schoolchildren than congenital malformations and all the circulatory, genitourinary, infectious, and respiratory diseases together. The familiar and gloomy situation concerning children's teeth may have improved. Surveys showed that in 1958 only 12·8% of the 5-year-olds and only 5% of the 12-year-olds had no carious, missing, or filled teeth: the average number of decayed, missing, or filled teeth per child was 5·7 at 5 years and 5·5 at 12 years. The surveys showed that deterioration of the teeth was less in 5-year-olds but greater in 12-year-olds between 1953 and 1958 than between 1948 and 1953. " It is significant that during the period 1948 to 1958 sugar consumption per head in the United Kingdom rose from 88·3 lbs in 1948 to 103·1 lbs in 1953 and to 120·7 lbs in 1958." Propaganda for dental hygiene is increasing, but it is unlikely to reach as wide an audience or have so great an impact as advertisements like the one for " the sweet you can eat *between* meals ". The news about dental treatment is also unsatisfactory, and the shortage of school dentists is an old story.[3] The School Dental Service is at present able to treat little more than half the children requiring treatment. Many are treated by the general dental service, but even so " hundreds of thousands are neglected ". Moreover, until recently the net annual loss of whole-time dentists in the School Dental Service was made good by the recruitment of part-time dentists. But in 1959, for the first time, the number of new part-time dentists did not balance the number of whole-time dentists who retired or left the service. " Should this trend continue, the outlook for the school dental service will be even bleaker."

Concerning the mental health of the schoolchild, the situation is less clear. Between 1956 and 1959 developmental psychological defects noted by school doctors as requiring treatment increased by more than 50%, from 2·1 to 3·3 per 1000 inspections, and those classified as requiring observation increased from 5·9 to 7·1 per 1000. Disappointingly, the report does not try to discuss the real significance of these figures, but it does endorse the therapeutic value of child-guidance clinics, a view that some will question. No mention is made of school phobia, lately described as an " almost epidemic condition which has developed in recent years in this and other countries "[4] and which has excited much interest.[5]

Of schoolchildren in 1961 it might be said that *as children* they are apparently very healthy, being taller and heavier and freer from overt disease than ever before; but *as potential adults* they are less healthy than they could or should be. Their feet and teeth are in bad condition, and a high proportion have already acquired habits, such as smoking and overeating, which may to lead to disease, disability, and premature death in adult life. Moreover, on all sides they are encouraged to develop these habits; indeed, the maintenance of a fair slice of the national income depends on their so doing. As long as this is so, a health-education campaign, however widespread and competent, can do little more than appease a few consciences, and perhaps save a few lives. In this connection, one of the most interesting chapters of the report describes how nurses, health visitors, and doctors are extending their contracts with schools in some areas and are giving health education its widest meaning.

1. The Health of the School Child: Report of the Chief Medical Officer of the Ministry of Education, 1958 and 1959. H.M. Stationery Office, 1960. Pp. 231. 10*s*. 6*d*.
2. See *Lancet*, 1959, i, 237.
3. *ibid*. 1960, ii, 861.
4. Pirrie, D. *Brit. med. J*. 1960, ii, 1164.
5. See *Lancet*, 1960, i, 270; *Brit. med. J*. 1960, ii, 848.

Apart from health education, the other big function of the School Health Service is the discovery of defects and diseases that require treatment or observation. Since many of these defects and diseases are nowadays minor, or not always harmful, doctors are likely to disagree about what is abnormal and what requires treatment. One of the perplexing features of the report is the enormous variation in diagnosis from district to district and from doctor to doctor.

For instance, the incidence of skin disorders per 1000 children examined is reported as 1·20 in Rutland, and 100·94 in Salford; and in case it is thought that skin disorders must be commoner in industrial areas, the comparable figure for Tynemouth is 7·65 and for Exeter 61·31. In Southampton, visual defects were found in 224·42 per 1000 children examined and in Eastbourne in 209·56; but in Buckinghamshire they were found in only 46·82 and in Darlington in 38·72. In Rochdale 52·46 per 1000 children examined were found to squint, but in Brecon only 0·80. Otitis media was reported in 188·38 per 1000 children in Salford and in 0·27 in Darlington. Heart-disease was recorded in 45·41 per 1000 children examined in Southampton, but in only 1·81 in Southend.

Seven school medical officers examined 2000 children each, and one of the things they noted was the number of children with cervical glands *requiring treatment*. Their respective figures were 0, 2, 2, 47, 1, 2, 11. What treatment was advocated, and whether or not it was given, is not stated.

There is detailed information, however, about tonsillectomy. The proportion of children who had had their tonsils removed varied extraordinarily from district to district. In Huntingdonshire 42·2% of 14-year-old children had had the operation, but in the neighbouring county of Bedfordshire the figure was only 9·2%. The proportion of tonsillectomised children in the towns also varied inexplicably. In Blackpool, for instance, the figure was 35·6%, in Bath 35·0%, but in Peterborough 5·9%. In Kingston upon Hull it was 36·2% and in Carlisle 34·1%, but in Barnsley 3·4% and in Swansea 1·3%.

These figures, and many others in the report, suggest either that there are hundreds of thousands of children in the country in need of tonsillectomy and other treatment who are not getting it, or that hundreds of thousands of children are being submitted to unnecessary operations and treatment by other methods. Of the difference of opinion about cervical glands, the report says: "The factors giving rise to these anomalous findings are worth further study, or at least discussion between the medical officers concerned." Surely, when the recurring question of "what requires treatment?" becomes more and more difficult, this is an important matter demanding a more urgent approach.

## THE IMPORTANCE OF BEING TRIGONOMETRIC

STEREOTAXIC brain surgery involves peculiar difficulties.[1] Owing to the variability between different human brains in their internal proportions, the aim at best is based on a statistical approximation. Moreover the operator must relate the approximated brain maps [2 3] to external landmarks which he must either find or make. Most of the operations have been performed for dyskynesia, and the targets have usually been the globus pallidus and nucleus ventralis-lateralis of the thalamus; and the operators have mostly opted to make on the skull external landmarks that are related to the targets. Either a frame is applied with radio-opaque grids, or telescopic rings are manœuvred into the correct position by screening with ethyl iodophenylundecanoate in the ventricle as preliminary guide to the target. The method of using a grid with fixed tube-frame distance has been applied to Leksell's stereotaxic frame by Walsh.[4] Donaldson and Gillingham [5] undertake manipulation under screening with target rings on either side of the head, choosing skull points from a series of lead marks by trial and error for the sagittal line. Hughes [6] employs a fixed-grid method for his own adaptation of the Leksell instrument. Bennett [7] uses a combination of the two methods, manipulating a grid into position by screening and then by a series of radiographs until the central ray passes within 1 cm. of the target. Many other modifications are practised by individual surgeons. The original reference-points of the external meati and infraorbital margins are not suitable for aiming at high midline structures; and these are used, if at all, for preliminary line-up. But these reference-points can be used for some other targets—for example, structures in the temporal lobe near the meatus or at the frontal base near the base line.

The crucial reference is the central ray, from which all measurements must be made. The other rays are all divergent from it, so measurements on the film must have a fraction subtracted. If, for example, the tube is 5 feet from the film, and the target in the brain is 6 inches from the film, 10% must be subtracted from the measurement. With a measurement of 2 cm. the error would otherwise be 2 mm. The trigonometry involved is extremely simple, though it may be necessary to use the posteroanterior views to determine the distance of the target from the *lateral* film, and vice versa. Measurements in the plane of the target parallel to the film are valid with only the simple proportional correction. No amount of manipulation can obviate the necessity to refer distances in different planes to differing corrections. Within 1 cm. of the central ray with a long tube-film distance, the error may be less than 1 mm. but at any distance complete correction can be made with ease by simple arithmetic.

So far few operators have used anyone else's apparatus without some modification of their own. Surgical instruments are often individually made, and this adds greatly to the cost. It seems unlikely that in the present state of stereotaxic surgery a standard instrument could be produced; but there might be a case for manufacturing a widely adaptable form of the Leksell apparatus. The criteria are clear—accuracy of the frame; a fixed tube-film distance; easy identification of the central ray, probably by double grids; and a quick method of sinking studs into the skull for seating the frame back in the same position on a subsequent occasion. In view of the asymmetry of many calvaria there is much to be said for adhering to Reid's line as the basis for preliminary alignment (with the central ray at a higher level). However one may dislike standardisation, pooling of technical methods at the commercial end, as with other radiographic equipment, seems to be indicated.

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Dr. EDITH SUMMERSKILL, who has been leading for the Opposition on health subjects in the Commons, has been created a life baroness.

1. *Lancet*, 1960, i, 212.
2. Spiegel, E. A., Wycis, H. T. Stereoencephalotomy. New York, 1952.
3. Schaltenbrand, G., Bailey, P. Introduction to Stereotaxis with an Atlas of the Human Brain. Stuttgart, 1959.
4. Walsh, L. S. *Brit. J. Radiol.* 1960, **33**, 761.
5. Donaldson, A. A., Gillingham, F. J. *ibid.* p. 757.
6. Hughes, B. *J. Neurol. Neurosurg. Psychiat.* 1960, **23**, 351.
7. Bennett, A. M. H. *Brit. J. Radiol.* 1960, **33**, 343.

## Points of View

# PLANNING THE WORK OF A NEW HOSPITAL

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WITHOUT clear ideas of the functions to be performed in a hospital, the new buildings will be disappointing however good the architects. Powell (1959) is reported as saying that the most important thing he and his associates have tried to build into their hospital at Swindon is " a new attitude towards the patient ". The first forty years of this century, he added, tended to produce hospitals designed more for the specialist than for the patient he was treating.

The outlook of our profession has been criticised often. Gregg (1957) said that " there are plenty of M.D.s in this world but not enough real doctors ". Ffrangcon Roberts (1952) pointed out that medicine is permeated by the *idea of progress*—" the feverish consciousness of the dynamism of medicine which is almost universally felt in the teaching hospitals "—and by an interest in the processes of disease rather than in their effect on conduct and feeling. Confirming many of the opinions of Roberts, Lees (1960) goes on to argue that " public authorities have undertaken to extend health services at the very time when, from the economic point of view, they can do least good ".

These criticisms show a desire for change in many aspects of medical work, and we should begin, I believe, by agreeing that we ought to enlarge our aims in at least three directions: (1) by giving more attention to alleviation of the many diseases which we cannot cure, (2) by taking more account of the relation of illnesses to the personality and emotions of the patient, and (3) by taking greater interest in prevention. These extensions are hindered by the cleavages between general practitioners, hospital doctors, public-health doctors, and research-workers.

### ALLEVIATION

Each patient has the right to expect that we shall do all we can for him; and if we try to do this in an individual way there need be no fear of the techniques of diagnosis and treatment being neglected. The situation is one which we may understand best when we treat our relatives or our friends, because we cannot then seal off the matter from our minds.

Continued study of the results of hospital care seems to me essential. Ferguson and MacPhail (1954), reporting on the condition of 705 men who had left an acute medical ward in one or other of two Scottish hospitals three months and two years previously, found the results rather disappointing; but they were able to improve on these results by various social and medical means applied after discharge from hospital. After a similar study at Oxford Brown and Carling (1945) wrote:

> " Only a small proportion of patients are completely and speedily cured as a result of admission to a medical ward. For the majority of them it constitutes a short episode in a long period of disability, and unless in-patient treatment and after-treatment are closely integrated, much of the benefit of the stay in hospital may be lost."

These surveys and the comparable ones by Beck et al. (1947) and Fry (1959) required the cooperation of general practitioners, hospital doctors, and public-health doctors. If the necessary continuous care of patients and the necessary prevention of disease are to be achieved this cooperation must become close and permanent. At present the administrative separation of doctors is an excuse for much mental inertia. A Parkinsonian law might be stated thus: " Our best protection against doing what we should is a bustling use of a familiar routine."

Pointing out that " the function which the good practitioner can in fact perform better than the best of hospital groups is personal medical care—looking after people as people ", Fox (1960) also says that " the practitioner's usefulness and professional status depend on his being well informed; and in the modern world close association with the hospital is therefore a condition of his professional survival ". Similarly Forsyth and Logan (1960), believing that there are already more beds in acute hospitals than would be required if practitioners could take more complete care of their patients at home, say that one means towards this end is much closer cooperation of family doctors and hospital doctors.

Some examples of past errors in ignoring opportunities of helping patients have now been made clear: instead of being shunned and neglected, the " old chronics " and " old bronchitics " receive intelligent and very valuable assistance. But there are opportunities which we have not yet taken. The surveys of results of hospital care show how temporary much of the benefit is, and how necessary it is for the hospital doctor and the family doctor to continue to use all possible means to enable the patient to lead the life he desires. A comprehensive plan of rehabilitation is followed more fully in some branches of work—such as geriatrics, pædiatrics, and the care of patients with tuberculosis and coronary thrombosis. But in all branches advantage could be obtained from better mechanical aids and freer association with family and public-health doctors and with almoners and social workers.

When the broader view is taken of the hospitals' duty to patients, many experimental arrangements deserve further study. Thus Stallworthy (1960) gives reasons for thinking that, by supplementing ward beds with beds in an annexe where nursing and equipment are less elaborate, the acute general hospital of tomorrow could be much smaller and more efficient. Likewise Ralston (1960) describes a " continuation " unit attached to Kilmarnock Infirmary. At Whittington Hospital an alternative experiment has been tried by the matron: though surgical patients are kept in the same ward until they go home or to a convalescent unit, the ward staff is reorganised in such a way that nurses give their skilled attention to patients who need it, and the comfort and guidance of other patients is in charge of suitable untrained women (of a grade not yet named) under supervision of the ward sister.

Wherever any new scheme is attempted, thought is required on the arrangement of space in rooms and wards, the siting and layout of outpatient and other departments, the nature of all types of furniture, bedding and clothing, and many aspects of nursing. One of the preparations for a new hospital should be the creation of a number of enthusiastic study teams. Even to deal intelligently with such well-established problems as hospital infection, doctors and nurses must bring newly furnished minds

to newly furnished hospitals. They cannot leave the planning all to others.

### ILLNESS AND PERSONALITY

Besides material alterations in means of treatment, there is the need for doctors to find time to get to know more of the personality and life of their patients, so that medical attention shall be more made-to-measure and less reach-me-down.

The ability to diagnose mental or emotional disorder needs a careful method of interview which is quite different from the limited personal contact and the lengthy consideration of tests of physical fragments of the patient which occupy much of the time of hospital doctors. Denis Hill (1960) remarks that " the organic causal hypothesis of medicine has resulted in a situation where, from its exclusive use, nearly half the ills of man remain outside consideration ". The conventional medical education prepares us very little to accept ideas about the interaction of mental and physical changes, and some members of our profession in their earlier years might in point of fact be more at home in veterinary work than in human medicine; yet even there they might be surprised at the amount of attention that may be given in a zoological hospital to gaining the animals' confidence before operation or other treatment.

In using the great gifts of medical science we have produced a rather heavy, doughy result, and we need to infuse something more of the human spirit into our work and our view of our patients.

### PREVENTION OF DISEASE

Again because of the present state of medical education, the clincian's interest starts only after disease has started; and more attention to prevention is certainly needed.

To widen our outlook in this direction we need, surely, to know the human environment of the district around our hospital—as regards living and working conditions, traffic in the streets, feeding, and amusements—and we must be prepared to find out whether life and work contain a major preventable factor in the maintenance of illness—such as Ferguson and MacPhail (1954) discovered in a quarter of the patients they studied. It is notable that the preventive method has been longer followed by the clinicians concerned with tuberculosis and venereal diseases than by those in most of the other branches; and the reason probably is that in these two specialties there has been more cooperation between hospital doctors and public-health doctors. It is certainly old-fashioned for those who work in hospitals to limit their knowledge of medical work to the unnatural surroundings of wards and outpatient departments.

It was because of the narrow vision of most of our profession that local authorities needed to set up separate establishments and staffs for the preventive work of the clinics. The valuable system of caring for diabetic and gastric patients in their homes by the combination of general practitioners and welfare workers with the advice of hospital doctors was pioneered by medical officers of health, especially by Greenwood Wilson in Cardiff (Wilson 1951).

### TOWARDS A PRACTICAL SCHEME

If hospital doctors are expecting new hospitals to be built, the least they can do is to make sure that they will be ready with new ideas to mould, or at any rate to match, the new buildings. It would be a highly profitable investment for regional boards to attach a very small medical and clerical team to the medical committee of those hospitals which are to be rebuilt, to decide both ends and means. Such a team could be supplied by seconding a member of the senior medical staff of the hospital or by making an appointment for a number of years of someone to go from one hospital to another in succession. But the mainspring of thought should come from the medical committees, and they should think of both the present and the future.

Hospital doctors must not only face each other round the committee table, but turn about and face the community they work for and the other branches of profession. I believe we must agree with the Duke of Edinburgh (1959) that there is an overall deficit in our efforts. " Is the medical profession content ", he said, " only to fight disease and disability and accept the negative definition of health as someone who is not actually ill? " Medicine as we practise it—and we practise it very well—is not quite enough.

Medical committees should form subcommittees or groups for acquiring knowledge or forming opinions and decisions on the following subjects:

1. *The community.*—From the medical officers of health knowledge should be obtained of the population (including immigrants); of housing, parks, and recreation grounds; of occupations with health hazards; and of the road system, its traffic, and the pattern of road accidents in time and place.

2. *The protective services of public authorities.*—Again from the M.O.H., facts should be ascertained about the network of antenatal clinics and school clinics, and about the inspection of houses and of premises connected with food. The local pattern of defects in health and in environment should be understood. Also, the system of district nurses and health visitors, social workers, and almoners should be known.

These two surveys should help to emphasise that a hospital is a part of its community. A defect of many teaching hospitals in big cities like London seems to be that they teach scientific medicine in a social vacuum.

3. *Inpatient treatment.*—The liaison committee representing all kinds of doctors in the area should start with a survey of the results of treatment in their own hospital, as made in Glasgow by Ferguson and MacPhail. From that would develop means of improving these results by the action of general practitioners, medical officers of health (with district nurses, health visitors, and home helps), and hospital doctors, and almoners.

On home care Godber (1956) wrote: " Hospitals have their place in contributing to home care and are to be regarded as an expert supporting service—not as something apart from, or above, medical and allied services outside their walls." The liaison committee should consider the number of hospital beds needed for their area in the light of the survey in Barrow-in-Furness (Forsyth and Logan 1960) and should consider the arrangements for home care which they can make for various types of patients in their area. In assessing the proportion of illness that should be treated in hospital rather than at home the extent to which women are away from home and at work must be remembered.

This would perhaps be the occasion for hospital doctors and general practitioners to discuss their proper working relations to one another. For the patients' benefit it is necessary that general practitioners should bring their

knowledge to the hospital bedside and should receive in exchange some of the scientific knowledge of the hospital. Walker (1960) has suggested:

"That machinery should exist whereby the highly specialised knowledge which the G.P. has of his patients should be at the disposal of the hospital consultants, on request, for a fee, during the period in which a patient is in hospital. In other words, that is to say, a hospital domiciliary visit service with the roles reversed. . . . The scheme would give the G.P. a sense of responsibility within the hospital walls instead of just being a visitor and possibly a nuisance. It would also help to obviate the impression held by some that G.P.s hand over their patients to 'superior beings' when they send them to hospital. The cost to the Exchequer of such a scheme would be more than balanced by the increase in knowledge and skill which the G.P. would acquire as a result of these contacts, consequently reducing the number of hospital referrals made."

At any rate, space and place must be found for general practitioners in hospitals.

Within the hospital the matters to be considered include the size, shape, and internal division of wards—if that term is still retained for the organisation of space in a nursing unit of a hospital—with the lighting, decoration, furnishing, and supply of inward and outward services. Reasoned choice in these matters is offered and illustrated in such publications as that of the Nuffield Trust (1955). A reorganisation of nurses is being made by the General Nursing Council, and I have already mentioned experiments in the care of patients after operation. Another requirement is provision for patients who come to hospital for some days of investigation. This is included in the plan of reorganisation of ward staff by the matron of Whittington Hospital, and it illustrates the need for discussion between the matron and the medical committee.

4. *Outpatient treatment.*—The liaison committee is needed also to consider whether the attendances at the outpatient department are sufficient, excessive, or insufficient for the circumstances of the community. If too much time seems to be spent by patients in the department, the careful study of the Nuffield Trust (1955) should again be considered. This records that both time and space were saved when as far as possible a consultant dealt completely with each patient in turn, before considering the next.

Rooms are needed where outpatients can recover—under nursing supervision—from minor operations, where lumbar puncture or marrow puncture can be done; and where series of specimens can be taken—e.g., for glucose-tolerance tests. There should be a small laboratory for immediate tests.

## GENERAL CONCLUSIONS

The changes which are beginning are of a familiar general pattern. The close military formation of one period requires to change to open order in the next; the ritual of religion and the scholasticism of education require to be modified so that in changed circumstances the basic aims of the professions can still be pursued.

The scientific method has given very great assistance to medical work during the last century, but it can be applied only in a highly selective way to phenomena which can be measured by the scientific means of the time. Science is exclusive in a manner that seems to say "what I can't weigh isn't knowledge". That explains why the scientific method is applicable to only a very small sector of human life and should be a means, and not the only means, of pursuing the aims of medicine.

It may be asked how time can be found for expanding aims and interests when everyone in hospitals is so very fully occupied with things as they are. An astringent answer may be found in the Parkinsonian law which I propounded above; but more encouragingly I think that, if the expanded interests are believed to be worth while, a reduction in some present activities will be justified.

An area in which time might be saved is what Roberts (1952) called "the unlimited field now open for the satisfaction of curiosity and ambition". In this field is built a complicated façade of borrowed physiology, biochemistry, and the pride of clinicians in this false front seems to distract their attention from the full benefit that their own knowledge, skill, and wit might confer on their patients.

To some extent their attitude is the result of over-conscientious attention to a reform that began, perhaps forty or so years ago, with the slogan "No treatment without a diagnosis". As a result, symptomatic, palliative, and individual treatment of patients who suffer from complaints which cannot be "diagnosed", or for which a complete cure is not known, is greatly ignored. Diagnosis does, of course, include a supremely valuable step in the process of deciding that a patient requires a certain form of treatment and has a certain prospect as regards his complaint. But a cut-out is, I think, needed to prevent this very complex mental process from continuing in cases where a diagnosis—in the practical sense of an indicator of effective treatment—cannot at present be made. This restraint is gained by good clinicians sooner or later, and gives them the time to make their own study of unsolved problems.

It is frequently and truly stated that specialism within medicine has been necessary for the advances of the past hundred years; but there comes a time when the divisions of specialism cause more gaps than they fill. *The Lancet* (1960) recently drew attention to dangers to patients from lack of medical knowledge in surgical wards and vice versa; but where the higher specialties are highly cultivated the risks may be greater still, and the specialty may be cultivated at the expense of the patient.

Until a few years ago interest in medical education centred on methods of teaching, but latterly more thought has been given to the kind of person that a doctor ought to be. I conclude with the words of Newman (1957) who sees education as the safeguard of the future provided the one thing that is essential is maintained—"the professional spirit of putting the interest of the individual patient above the claims of gain, of fame, of research, and of the State".

## REFERENCES


Beck, I. F., Gardner, F. V., Witts, L. J. (1947) *Brit. J. soc. Med.* **1**, 197.
Brown, M., Carling, F. C. (1945) *Brit. med. J.* i, 478.
Edinburgh, Duke of (1959) *Canad. med. Ass. J.* **81**, 116.
Ferguson, T., MacPhail, A. N. (1954) Hospital and Community. Nuffield Provincial Hospitals Trust. London.
Forsyth, G., Logan, R. F. L. (1960) Demand for Medical Care. Nuffield Provincial Hospitals Trust. London.
Fox, T. F. (1960) *Lancet*, i, 743.
Fry, J. (1959) *Brit. med. J.* ii, 1322.
Godber, G. E. (1956) *Practitioner*, **177**, 15.
Gregg, A. (1957) For Future Doctors; p. 48. Chicago.
Hill, D. (1960) *Brit. med. J.* i, 917.
*Lancet* (1960) Leading article, i, 1229.
Lees, D. S. (1960) *Lloyds Bank Rev.* April, p. 26.
Newman, C. (1957) Evolution of Medical Education in the Nineteenth Century. London.
Nuffield Provincial Hospital Trust (1955) Studies in the Functions and Design of Hospitals. London.
Powell, P. (1959) *Sunday Times*, Nov. 1.
Ralston, G. J. (1960) *Lancet*, i, 177.
Roberts, F. (1952) Cost of Health. London.
Stallworthy, J. A. (1960) *Lancet*, i, 103.
Walker, A. P. (1960) *Brit. med. J.* i. suppl. 179.
Wilson, J. G. (1951) *Month. Bull. Min. Hlth P.H.L.S.* **10**, 204.

## Special Articles

# BACTERIOLOGICAL INVESTIGATION OF EXHAUST AIR FROM HOSPITAL VACUUM CLEANERS

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THE domestic broom was often believed to be responsible for distributing infection in the days before the vacuum cleaner took over the task of removing dust from hospital floors (White 1936, Brown and Allison 1937, Crosbie and Wright 1941, and others). Of the two, the vacuum cleaner is potentially the greater danger. A powerful stream of air sweeps through the reservoir which it contains; and should this reservoir fail to hold the material drawn in, infection could be spread far more thoroughly than by any broom, and not only in the confines of the ward being cleaned. Such dissemination was shown by Bate and James (1958) in outbreaks of gastro-enteritis due to *Salmonella typhimurium* in a children's ward, the dust-bag of a suction-polisher being the only discoverable source of infection. That reports of similar outbreaks are few constitutes almost the only testimony to the safety of the modern vacuum cleaner, and the absence of more direct evidence (apart from that supplied by Rogers [1951] in respect of one particular machine) causes widespread uneasiness among those called on to purchase or to supervise the operation of hospital vacuum cleaners, and among those concerned with the control of hospital infection. To most of these, this aspect of vacuum-cleaner performance must be of the first importance, yet no reference to it can be found where it might be most expected—namely, in the British Standard Specification for Electric Vacuum Cleaners for Use in Hospitals (B.S. 3028 : 1958).

This deficiency was apparent to the division of hospital facilities of King Edward's Hospital Fund for London, when, in 1958, it asked me to devise and make investigations to determine the relative filtration efficiency of a number of different types of vacuum cleaners and suction polishers used in hospitals. The division made arrangements for eleven manufacturers to loan machines for tests; tribute is due to all of them for their ready cooperation in the investigation.

### Types of Cleaner Investigated

*Cylinder-type cleaners.*—These are horizontal cylinders, in which the dust is usually received into a paper bag. Freed of gross dust, the air is filtered through a cloth bag (which also acts as a support for the paper bag) and through at least one other filter, either before or after the air-impeller.

*Tank or canister-type cleaners.*—Dust is received into a metal tank, from which the air is drawn out through a cloth filter suspended in or over the tank.

*Suction floor-polishers.*—These are rotating-brush polishers in which centrifugal dispersal of dust is counteracted, and some cleaning is done by air suction through the hood surrounding the brushes. Dust is collected in a disposable paper bag held inside a cloth bag which is suspended from the handle of the machine.

Table I summarises the relevant features of the performance and construction of the machines.

### Methods

*Bacterial Content of Exhaust Air*

To provide standard conditions for examination of the exhaust air, arrangements were made to collect 20 c.ft. volumes from each machine in a collapsible polyethylene reservoir mounted over a slit-sampler (fig. 1). Details of the construction and operation of the apparatus are described elsewhere (Bate 1961). Cleaners were examined after being in regular daily use in the wards of the hospital for a month, and again three months later. Each time three 20-c.ft. volumes were collected, and from each a 5-c.ft. sample was passed through the slit-sampler.

*Air Disturbance*

Many cleaners discharge their exhaust air in the form of a high-velocity jet, having an obviously disturbing effect on unswept floor dust and the surrounding air. This disturbance was studied by allowing the exhaust from each vacuum cleaner to discharge into a small closed room for four minutes, and estimating the bacterial content of the air, by means of the slit-sampler, before and at intervals for ninety minutes afterwards (for details see Bate 1961).

TABLE I—CHARACTERISTICS OF THE CLEANING MACHINES TESTED

| Cleaner | Type | Air displacement (c.ft. per min.) | Closed vacuum (inches water gauge) | Suction power (ft. lb. per sec.) | Filters: Material | Filters: Area (sq. in.) | Filters: Pore diameter (microns) | Dust container | Exhaust |
|---|---|---|---|---|---|---|---|---|---|
| A | Cylinder | 63 | 50 | 61 | 1. Fabric bag | 270 | — | Paper bag | D.A. |
| | | | | | 2. Carded cotton and gauze | — | — | | |
| | | | | | • 3. Carded cotton | 1207 | — | | |
| B | | 60 | 59·5 | — | 1. Linen bag | 353 | — | | Diffused |
| | | | | | 2. Flock-covered paper disc | 20 | — | | |
| C | | 60 | 44 | 72 | 1. Cloth bag | — | — | | Open |
| D | | 58 | 60 | 61 | 1. Cotton sateen bag | 210 | — | | D.A. |
| | | | | | 2. Flannelette, carded cotton, and gauze | 35 | — | | |
| | | | | | • 3. Toughened filterpaper | 41·5 | — | | |
| E | | 50 | 39 | 112·5 | 1. Cotton drill bag | 360 | — | | Open |
| | | | | | 2. Compressed paper | 1440 | 0·5–1·0 | | |
| F | | 140 | 67 | — | 1. Kraft paper | 800 | 1·0 | | Diffused |
| | | | | | 2. Mitten flannel | 400 | — | | |
| | | | | | 3. Glass fibre | 260 | 0·3 | | |
| G | | 71 | 59 | 97 | 1. Corrugated cotton/sateen disc | 260 | — | | D.A. |
| | | | | | • 2. Toughened filterpaper | 41·5 | — | | |
| H | Tank | 65 | 59 | 95 | 1. Fabric sleeve | 300 | <1 | Tank | D.A. |
| | | | | | 2. Fabric sleeve | 52 | <1 | | |
| I | | 94 | 59 | 128 | 1. Fabric sleeve | 300 | <1 | | D.A. |
| | | | | | 2. Fabric sleeve | 52 | <1 | | |
| J | | 52 | 42 | — | 1. Grey imperial cotton sleeve | — | — | | D.A. |
| | | | | | • 2. Calico (bleached) bag | — | — | | |
| K | Suction polisher | 65 | N/A | N/A | Satin drill bag | 600 | — | Paper bag | N/A |
| L | | 60 | N/A | N/A | Fabric bag | 288 | — | | N/A |
| M | | — | N/A | N/A | Fabric bag | — | — | | N/A |

Air displacement and closed vacuum measured with all filters in place, at machine inlet.
Suction power according to B.S. 3028 : 1958.
N/A = figure not applicable; — = information not received; • = external filter; D.A. = diffuser available to order.

## Results

*Bacterial Content of Exhaust Air*

Colony counts from the samples of exhaust air are shown in table II. These figures show that, under laboratory conditions, nine out of ten vacuum-cleaner exhausts contained less than 1 bacteria-carrying particle in 5 c.ft. The tenth machine yielded air in which a colony-count of $2^1/_2$ was found in 5 c.ft. This

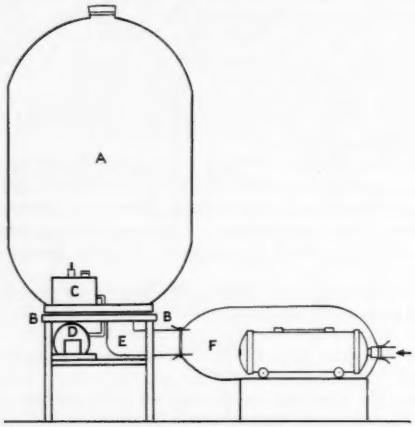


**Fig. 1—Diagrammatic cross-section of the apparatus.**
A—air reservoir; B—table carrying slit-sampler, C, and its air-pump, D; E—duct leading to reservoir, and F—receiving tube containing cleaner under test.

machine had only a single effective layer of filtering cloth, the inadequacy of which was confirmed when examination showed the impeller to be coated with a layer of fine dust. The makers later provided a double-thickness filter for test, and the air from this contained less than 1 colony in 5 c.ft.

The air from the three suction floor-polishers contained some six times as many bacteria-carrying particles to the cubic foot as did that from the nine best vacuum cleaners. Some of these particles may have passed through the paper and the relatively coarse fabric bags which constitute the dust-containing arrangements on these machines, but some may have been deposited outside the bags while the machines were out of use, to be blown off again when they were switched on. No attempt was made to determine their origin.

*Air Disturbance*

A very sharp difference was observed between the amount of air disturbance caused by open-exhaust machines and by those in which the exhaust velocity is reduced by a diffusing device. All the tank cleaners, and all but two of the cylinder cleaners are, or can be, so equipped. The exhaust from suction floor-polishers is diffused and made imperceptible by the large cloth bag through which it is emitted.

TABLE II—COLONY COUNTS FROM EXHAUST SAMPLES

| Cleaner | Type | No. of colonies from samples | | | | | | Total at 30 c.ft. | Average no. of colonies from 5 c.ft. |
|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | | |
| A | Cylinder | 1 | 0 | 1 | 0 | 0 | 1 | 3 | 0·5 |
| B | | 0 | 0 | 0 | 1 | 0 | 2 | 3 | 0·5 |
| C | | 0 | 0 | 0 | 1 | 1 | 0 | 2 | 0·3 |
| D | | 1 | 0 | 1 | 1 | 0 | 1 | 4 | 0·7 |
| E | | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0·2 |
| F | Tank | 1 | 1 | 0 | 0 | 0 | 0 | 2 | 0·3 |
| G | | 1 | 0 | 1 | 0 | 1 | 0 | 3 | 0·5 |
| H | | 1 | 1 | 0 | 0 | 0 | 2 | 4 | 0·7 |
| I | | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0·2 |
| J | Suction polisher | 3 | 3 | 6 | 0 | 0 | 3 | 15 | 2·5 |
| K | | 7 | 1 | 2 | 3 | 1 | 3 | 17 | 2·8 |
| L | | 2 | 9 | 3 | 3 | 5 | 1 | 23 | 3·8 |
| M | | 4 | 0 | 4 | 6 | 6 | 5 | 25 | 4·2 |

Fig. 2 shows that operation of the open-exhaust machine causes an immediate rise in the number of bacteria-carrying particles in the room air. This subsides as the air becomes still again, but there follows a slow bacterial fallout (which lasts about an hour) due to the slow descent of fine particles which have been wafted to the upper reaches of the room. From a typical cleaner with diffused exhaust there is almost no disturbance, either immediate or delayed, and the curve follows closely that for the natural die-away of bacteria-carrying particles in undisturbed air.

## Discussion

From the investigations described, it seems reasonable to expect that the exhaust air from a properly used and maintained vacuum cleaner should not contain more than 1 bacteria-carrying particle in 5 c.ft. Except for the dust which is sucked from the floor, this exhaust air is likely to be many times purer bacteriologically than the air drawn in from the ward, and its bacteriological quality is, in fact, of the order suggested by Bourdillon and Colebrook (1946) as being suitable for neurosurgical operating-theatres and for dressing-rooms for the treatment of burns. When the bacterial content of the dust which is likely to be drawn in

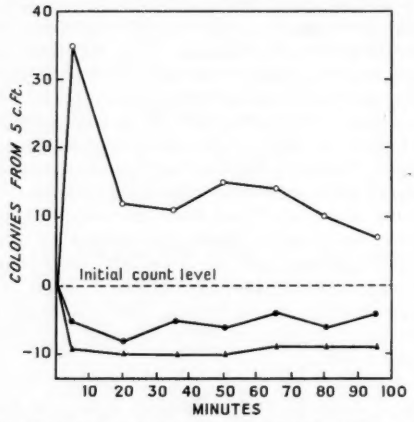


**Fig. 2—To show the alteration in bacterial content of room air after operation (during the first four minutes of the experiment) of cleaners with open exhausts (upper curve) and with diffused exhausts (middle curve), as compared with the natural die-away of bacteria-carrying particles under the same experimental conditions (lowest curve).**
The figures are means of those from five machines of each type.

from the floor is added to that contributed by the air, the enormous reduction in the possibilities of bacterial contamination from such machines becomes apparent. The discharge of air from them can be discounted as a cross-infection hazard, but only (and this qualification deserves repetition) so long as they are carefully maintained and properly used.

Absolute sterility of exhaust is an ideal pursued by one or two manufacturers who employ filtering material claimed to be of submicron pore size in one or more stages (table I). While this development is to be welcomed in general, one has to realise that in small machines the use of such material may not be possible without increase in size and weight, and reduction in air displacement. Those who prefer smaller and lighter machines may well feel that in view of their present creditable performance too much would be lost by insisting on absolute sterility.

The performance of suction polishers compares un-

favourably with that of vacuum cleaners in the matter of exhaust sterility, although all are fitted with paper bags which are intended partly as dust receivers and partly as filters to prevent contamination of the outer bags from within. These paper bags are far more vulnerable than are their counterparts enclosed in cylinder cleaners. Their emptying tends to be neglected, since lack of suction due to a full bag makes little difference to polishing efficiency. Consequently bags burst and infective material builds up inside the cloth covers. (Lest anyone should doubt that such material remains infective for long periods, I possess such a bag, from whose contents *S. typhimurium* can still be isolated three years after the infection entered the machine during cleaning of the floor of a ward in which infection with this organism had become endemic.) The outer covers can become contaminated from without when not in use, especially when the machine is stored in an insanitary cupboard. It would seem much safer to clean the floors first with an ordinary vacuum cleaner, and then to polish with a simple rotary machine without suction, than to run the risk of infection from dual-purpose machines. But if there is a need for them (and they have many adherents), they should be redesigned to the standard of the best vacuum cleaners, with filtering systems enclosed in metal or other impervious casings.

Disturbance of surrounding air by the exhaust of a cleaner is one way in which an otherwise well-constructed machine can promote cross-infection. A fast-moving exhaust jet is particularly liable to cause considerable increase in the bacterial content of the air of a room, especially when directed parallel and close to the floor, or, in the case of vertical exhaust machines, to walls and curtains. This can be abolished by some form of diffusing device, with which (since this is a requirement in certain industries) most cleaners can now be fitted. The ideal diffuser should be an integral part of the machine casing, but this is so in only two of the machines examined (B and F). Detachable diffusers are all too easily lost or jettisoned by operators who do not realise their importance.

The emptying of the contents of filled vacuum cleaners can contaminate the air and the staff performing that task. The disposable paper dust-bag has therefore given some advantage to the small cylinder-type cleaner, which is less suitable for the large hospital ward than are the heavier models with their greater power and larger tools. But this advantage can only be fully exploited by ensuring that the filled bags are changed before they have burst, leaving the inner cloth bag to pollute the air when it is shaken free of the dust and dirt it was never meant to contain. The wisest plan is to insist on the insertion of a clean bag every day before work begins; this is not an extravagance. The operational advantages of most of the larger cleaners are reduced by the lack of hygiene of their emptying arrangements. Cleaners F and I, in which the dust can be collected in paper containers, are exceptions. The best that can be said of the others is that when emptied well away from the wards they contaminate only the staff. If such machines are to continue in use, as indeed they must, their emptying should be the charge of some selected person, who is instructed how to cause the least possible contamination, and is provided with protective clothing and a paper-lined cylinder cleaner for periodical cleaning of the filters.

The alternative—which avoids many other difficulties in vacuum-cleaner operation and maintenance—is the use of central vacuum-cleaning systems, in which suction lines run from all parts of a building to a central dust-collector, filter, and air-impeller. This seems the most logical way of disposing of hospital dust, since it deals at one stroke with problems of maintenance and operation of numerous small vacuum cleaners, and removes the possibility of contamination by faulty machines, by the processes of emptying, and—not least—by failures of the human element in handling the machines. It is surprising that such systems are not as widely used in hospitals as in industrial and commercial buildings. Cost should not be a deterrent, but it probably is. In new hospitals it would be logical to adopt such a system as standard practice, and two London teaching hospitals are considering the installation of central systems in existing ward blocks. A central system was built into The Hospital for Sick Children, Great Ormond Street, in 1938, and another was installed two years ago in the new wing of the Royal Masonic Hospital, Ravenscourt Park. Through the kindness of the house governors, I visited both these hospitals during the investigation, and I was able to see the plants in operation, and to seek opinions from administrators, engineers, and operators, who were, in both hospitals, unanimously in favour of the system.

### Summary and Conclusions

A bacteriological investigation has been made into the quality of the exhaust air emitted by ten vacuum cleaners of types commonly used in hospitals, and three suction floor-polishers. The exhaust from all but one of the cleaners contained not more than 1 bacteria-carrying particle in 5 c.ft., which seemed unlikely to constitute a cross-infection hazard. One vacuum cleaner needed additional filtering material to bring the exhaust air up to the standard of the rest. The exhaust from all the suction floor-polishers was unsatisfactory in comparison with that from the vacuum cleaners, and if such machines are to continue in use, their filtering systems should be redesigned so as to emit air no less pure than that of the vacuum cleaners.

Room air is much disturbed by vacuum cleaners with open exhaust jets, and these should not be operated in hospital wards without some device to diffuse the outgoing stream of air.

Where dust is not collected into disposable bags, the emptying of vacuum cleaners is liable to contaminate the air and the staff doing this work. Manufacturers are urged to try to remedy this disadvantage.

It is suggested that central vacuum-cleaning systems should be incorporated as standard practice in the design and construction of ward blocks in new hospitals.

Mr. M. C. Hardie of the division of hospital facilities of King Edward's Hospital Fund, not only suggested this investigation but made all the arrangements with the manufacturers for the loan of cleaning machines, and he has supported me throughout in many different ways, for all of which I owe him much gratitude.

I must also thank the Wright-Fleming Institute of Microbiology of St. Mary's Hospital, and Dr. W. Howard Hughes in particular, for lending me the slit-sampler, and for providing laboratory space for a part of the investigation; and Prof. R. E. O. Williams for the interest he has taken in the work, for reading the manuscript, and for his helpful advice.

The manufacturers, who so kindly lent apparatus for test, must remain anonymous, but they may rest assured of my gratitude.

#### REFERENCES

Bate, J. G. (1961) *J. clin. Path.* **14**, 32.
— James, U. (1958) *Lancet*, ii, 713.
Bourdillon, R. B., Colebrook, L. (1946) *ibid.* i, 601.
Brown, W. A., Allison, V. D. (1937) *J. Hyg., Camb.* **37**, 1.
Crosbie, W. E., Wright, H. D. (1941) *Lancet*, i, 656.
Rogers, K. B. (1951) *J. Hyg., Camb.* **49**, 497.
White, E. (1936) *Lancet*, i, 941.

## The Wider World

# RELIGIOUS FAIRS AND FESTIVALS IN INDIA

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SOME 85% of the population of India are villagers with a rural pattern of life which has persisted from ancient times. In the State of Uttar Pradesh, the largest in India, with a population of some 70 million, the proportion is 87%, distributed in 111,722 villages. The average area of a village is 1 square mile. The villagers are intelligent but they are very poor, superstitious, and ignorant, and, of necessity, deeply fatalistic. Disease, disability, and mental illness are usually attributed to supernatural causes, and the dominating features of village life are religion and the family. Religious fairs and festivals have a special place in their lives and it was from these vast gatherings of pilgrims that the epidemics of cholera arose.

I have recently worked for twelve months in the State of Uttar Pradesh, the former United Provinces of Agra and Oudh. The State contains the largest number of centres of pilgrimages and fairs in India, and the great Kumbh and Ardh Kumbh fairs may attract as many as 5 million pilgrims. Last January I was fortunate enough to spend four days at the 1960 Ardh Kumbh held in Allahabad. During that time I lived in a magnificent tent that Akbar himself might have envied. Unlike Akbar I had electric light; but he, on the other hand, did not have the doubtful pleasure of being roused early in the morning by announcements and sacred music relayed by loudspeakers.

It is from this festival, above all others, that the great pandemics of cholera spread, the last outbreak being in 1948. So efficient were the medical arrangements at last year's Ardh Kumbh that they seem to me to be worthy of record.

### INTRODUCTION

Allahabad, formerly the capital city of Uttar Pradesh, has been held to be a sacred place by Hindus from the most ancient times.

A bathe at the confluence of the Ganges, Jamuna, and Saraswati (the lastnamed river is no longer to be seen), is considered sacred at all seasons of the year, but especially so during the month of Magh. The Magh Mela is an annual festival extending from about Jan. 1 to Feb. 15. Every twelfth year, when the planet Jupiter is in Aquarius (Kumbh) and the sun in Aries (Mekh) the Magh Mela becomes a Kumbh. Midway between each Kumbh, in the sixth year, is Ardh-Kumbh, —i.e., half Kumbh. These two festivals attract millions of pilgrims, besides large numbers of sadhus and fakirs. The Akharas, or corporate bodies of the various Hindu sects, attend Kumbh and Ardh Kumbh, and on the great festival days the leaders and followers of these sects march in formal procession to the river.

The last Ardh-Kumbh was in 1948 when there was a severe epidemic of cholera, with many hundreds of deaths, and the last Kumbh was in 1954. It was the scene of a tragedy when several hundred people were crushed to death in the largest gathering of pilgrims ever recorded, with over 5 million on the main bathing day. It was also the first occasion in India when a compulsory cholera inoculation scheme was enforced at a Kumbh.

It should perhaps be explained that, although there are five main bathing days, some orthodox pilgrims bathe daily throughout the month of Magh, and during that time they fast by day and abstain from eating grain. They live for the whole of this period along the banks of the river.

Each pilgrim on arrival is received by a member of an authorised class of local priests, known as pragwals, who has his groups of clients on his books arranged by castes and provinces or localities. The attachment of families to these priests is hereditary, and every pragwal family has its distinguishing emblem painted on a flag erected over the place where the panda, or priest, sits on the banks of the Ganges. Well-to-do pilgrims are accommodated by the pragwals in pukka houses in the neighbouring quarters of Daraganj and Kytganj. Those who are less well off stay in temporary thatched huts along the river bank. The vast majority live in the sandy plain under the open sky.

When the pilgrims arrive at the platforms of their respective pragwals, usually early in the morning, they are sent to the barbers' quarters for ceremonial shaving. The cut hair is collected, tied in gunny bags, taken away in boats, and thrown into a deep part of the river by the health authorities. After purification by shaving the pilgrim is taken by the priest to bathe, preferably at the Sangam or junction of the rivers which is clearly marked by a change in colour of the waters. At this time the devotee makes an offering to his priest as an essential part of the act of worship. Many pilgrims also offer gifts of milk or flowers to the rivers. After shaving, bathing, and the making of gifts, the main duty of the pilgrim is over; but few leave without visiting the sacred temples and shrines, and the stump of the Akshaivat tree cut down by the Emperor Aurangzeb. Finally the pilgrim returns to the priest to pay his parting fee, and he kneels before the priest who declares him to have performed meritoriously all the religious rites (suphal). He then returns to his home.

### MEDICAL ARRANGEMENTS

The camp area in 1960 extended over 35 square miles. On the main bathing day there was an attendance of 4 million pilgrims, who came by rail, road, and river. Those travelling by road came by bus, bullock cart (often double-decked), bicycle, or tonga, or on foot. The medical arrangements were the responsibility of the Uttar Pradesh State medical and health services of which Dr. K. M. Lal is the director. Local responsibility was deputed to Colonel A. Nand, assistant director, and the organisation fell under four main headings:

*Anti-cholera Inoculation*

At all approaches to the camp, on rail and road and river, a screen of twenty inoculation barriers was set up where all pilgrims unable to produce a certificate of recent inoculation were immunised. Each inoculation station was under the charge of a medical officer and was equipped with first-aid and medical tents in addition to the inoculation booths.

As the pilgrims were anxious to press on, any delay was liable to cause resentment, and the staffs had to work at high speed and with great tact. It was not uncommon for one station to perform over a thousand inoculations in a day, and they were so arranged that cases missed at one barrier would be picked up at another a few miles nearer to the city.

*Environmental Sanitation*

The whole Mela area was divided into seven circles, each under the separate command of an experienced medical officer of health. The success of the arrangements can best be described by the results achieved. It is literally true to say that there were no flies to be seen over the whole 35 square miles of the Mela area—not even on the stalls of the vendors of sweetmeats—and very few mosquitoes. Sanitation was by means of trench latrines in hessian enclosures, and their use was enforced by sanitary officers who took up duty at 4 A.M. and directed the pilgrims to use the latrines instead of the open ground. Sweepers were constantly employed in filling in the trenches with earth and lime, and cleansing the boards. Excreta deposited haphazard were immediately removed and the place was sprinkled

with lime. Rubbish and garbage were collected in pits and left to smoulder, except on windy days, until filled in at night.

We toured the whole area by jeep, by motor-boat, and on foot, and also inspected it from the Sangam watch-tower and the top of Akbar's fort. The appearance of cleanliness was quite remarkable; for not a single scrap of paper or waste material was to be seen at any time and the sandy beaches looked as though they had been recently swept. Close inspection of the latrines showed neither filth nor smell nor flies.

*Hospitals*

A central tented hospital provided a hundred beds equipped for major surgery, burns, and medical cases, with a plaster unit for fractures and a separate obstetric unit. On the visit of inspection a baby boy one hour old was produced, and the wards contained a patient with a suprapubic catheter, a fractured hip in a plaster spica, and a child badly injured in a railway accident, besides various lesser fractures put up in plaster. The enthusiasm of the young team of medical men and women at this hospital and the outlying hospitals was most encouraging. The various first-aid posts were manned by voluntary workers.

For infectious diseases the new and well-designed city hospital had been extended by a large tented unit, but fortunately this was not required. On the day of visit there were very few patients and most of these, including a case of smallpox, were local residents.

*Laboratory Arrangements*

Water-supplies were drawn from the city, from deep tube wells, and from shallow wells fitted with hand pumps in outlying areas. All sources of water, and also that of the rivers, including the Sangam or junction, were tested regularly in a central laboratory set up in the infectious-diseases hospital. This laboratory was also available for the bacteriological examination of stools and other pathological specimens.

### SAFETY ARRANGEMENTS: EXHIBITION

The disaster of 1954 was fresh in every mind and special care was taken to prevent a recurrence. The main avenues to the rivers were widened and fitted with crush barriers; watchtowers were erected at key points; and mounted and foot police were equipped with walkie-talkie apparatus. The central control room served as a control room for emergency medical purposes also.

A new feature was the large and well-designed pavilion containing a health and family-planning exhibition. Situated centrally, and picked out in coloured and moving electric lights at night, it was visible from a great distance and attracted many thousands of visitors. It was an interesting experience to pass slowly round with the pilgrims, watching the earnest way in which they listened to the demonstrators and studied the exhibits which dealt with many aspects of health and nutrition. Separate demonstration rooms were provided for men and women to be instructed in family planning. At the time of visit the doctors in charge of these rooms had crowded and attentive audiences.

### CONCLUSIONS

The efficiency of the medical arrangements may be gauged by the fact that no case of infectious disease arose at this Ardh Kumbh. In addition, the demonstration of environmental cleanliness, and the health exhibition, must have made a deep impression on the millions of visitors, many of whom came from rural areas. The greatest credit reflects on the skill and devotion of the medical team, all members of which worked for very long hours under taxing and exhausting conditions.

I should like to express to Dr. K. M. Lal, director of medical and health services, my deep appreciation of the privilege of being allowed to inspect in detail the health and safety arrangements; to Colonel Nand for his generous hospitality; to his staff for their courtesy; and to my colleague, Prof. B. G. Prasad, for being my guide and mentor.

# Conferences

## CEREBRAL VASCULAR DISEASE

FROM A CORRESPONDENT

THE third conference on occlusive cerebral vascular disease was held at Princeton, New Jersey, on Jan. 4–6, under the chairmanship of Prof. CLARK H. MILLIKAN (Mayo Clinic). These conferences, sponsored by the American Neurological Association and the American Heart Association, take place every three or four years and include 50–60 participants chiefly from neurological, neurosurgical, and vascular surgical centres, together with some neurophysiologists and other experimental workers.

### Investigation

New techniques for estimating cerebral blood-flow were described by Prof. GUSTAV NYLIN (Stockholm), Prof. PERITZ SCHEINBERG (Miami, Florida), and Dr. S. S. KETY (Bethesda, Maryland). Radioactive isotopes of iodine, phosphorus, and crypton have been used successfully; and it now seems possible to measure local directional blood-flow in certain areas of the brain. Ophthalmodynamometry seems to be a useful guide to diminished carotid blood-flow, but only when the flow is reduced below 50%.

Dr. ALBERT HEYMAN (Durham, North Carolina) had obtained additional help from the measurement of arm-to-retina circulation by the intravenous injection of fluorescein, and he showed impressive pictures of the intraretinal circulation.

Arteriography proved a thorny subject. Many thought it dangerous in cerebral vascular disease, but it was generally agreed to be essential where surgery was to be considered. The increasing emphasis on the importance of the extracranial vessels which supply the brain was well brought out; and Dr. H. L. BAKER, Jr. (Mayo Clinic) and Prof. WILLIAM FIELDS (Houston, Texas) suggested that aortography, intravenously, retrogradely through the brachial artery, or directly through the subclavian artery, was the best method of showing up these vessels, and particularly the mouths of the vertebral arteries. It was agreed that serious complications must be expected in 0·08% even in the best hands, and that expert surgical help should be immediately available to deal with these.

Some doubted the ability of neurosurgeons to operate successfully on major arteries, but Prof. FRANCIS MURPHEY (Memphis, Tennessee) declared that these were among the easiest operations he had undertaken. Full and complete studies were essential if all the lesions present were to be located, because multiple occlusions seemed to be characteristic of cerebrovascular disease.

Prof. SOL SHERRY (St. Louis, Missouri) described the fibrinolytic activity of normal blood and showed that in the brain the greatest release was connected with the pia mater. Although studies had shown that this thrombolytic activity could be changed by electroconvulsive therapy, pneumoencephalography, pyrogens, and frank ischæmia, no change had been found generally in cerebrovascular disease.

Dr. E. C. HUTCHINSON (Stoke-on-Trent) said that vertebral artery occlusion was often unsuspected and showed some excellent necropsy material. All the arteries of the neck could be clearly demonstrated by retrograde aortography through the brachial artery, but he did not think this technique adequate for the cerebral circulation. For the most complete pictures he preferred direct puncture of the subclavian and of the common carotid arteries under general anæsthesia. He had had no deaths among 115 patients, but 12 had had complications: pneumothorax in 1, pulmonary hæmatomas in 4, and worsening of the neurological deficit in 7.

Prof. W. S. FIELDS (Houston, Texas) and Dr. J. F. TOOLE (Philadelphia, Pennsylvania) showed striking arteriograms which underlined the fact that lesions were often multiple and

that reversal of flow down and across from one vertebral artery to the other was commoner than is generally realised.

### Treatment

In the case of anticoagulant therapy Prof. C. MILLER FISHER (Boston, Massachusetts) described a national project for patients with incipient strokes, progressing lesions and cerebral embolism. It had so far been found that reduction of cerebral emboli was significant with anticoagulant therapy; and the results in progressing strokes were encouraging. It was generally agreed that anticoagulant therapy significantly reduced the number of transient focal ischæmic attacks.

Dr. A. BARHAM CARTER (Ashford, Middlesex) defined the indications and contraindications for this treatment in progressing strokes; he thought that phenindione was a safer anticoagulant than coumarin.

The premature introduction of badly standardised fibrinolytic agents to the American market was criticised by many speakers; but it was hoped that further work would prove this type of treatment beneficial.

Prof. IRVING S. WRIGHT (New York) and his associates thought anticoagulants had a place in the long-term treatment of completed strokes; their series suggested that protection from further cerebral infarction, from pulmonary embolism, and from cardiac infarction could be obtained without hæmorrhagic complications. But Dr. ROBERT BAKER (Los Angeles, California) found the contrary in a similar series, with increased cerebral hæmorrhage and cerebral infarction in the treated patients.

Anticoagulant therapy has been shown to be of use in transient and progressing strokes, will protect against pulmonary infarction, but is dangerous in hypertensive patients and seems to be of little use after the stroke is completed.

Dr. M. E. DEBAKEY and Dr. E. S. CRAWFORD (Houston, Texas) pointed to the difficulty of selecting patients for surgery because more than one occluding lesion often coexists in the same patient; but they reported some remarkably impressive results in incomplete and complete lesions of both the carotid and vertebral vessels.

## Medicine and the Law

### Medical Cases on Industrial Injury Insurance

THE National Insurance (Industrial Injuries) Act 1946, which came into force on July 5, 1948, introduced for the first time a comprehensive system of State insurance for accidents at work. In general, all employees must be insured whether or not their employment is of a kind which would normally be regarded as "industrial". Benefits are paid under section 7 of the Act where an insured person suffers personal injury caused by an accident arising out of and in the course of his employment, or, if because of the nature of his employment he contracts a "prescribed disease" (section 55).

A claim for benefit is submitted in the first instance to a local insurance officer who investigates the facts. As part of his investigations, the insurance officer may refer any question of fact to "local referees" (representative of employers and labour) or to a doctor. Having ascertained the facts, the insurance officer will normally give a decision himself, but he may refer the case to a local appeal tribunal; in any event, certain "special questions" must be referred to the Minister, and claims for disablement benefit must be referred to a medical board. A decision of the Minister may be challenged on law, but not otherwise, in the High Court. If a claimant is dissatisfied with the decision of a medical board, he may appeal to a medical appeal tribunal consisting of a chairman and two doctors.

When a decision has been given by the insurance officer himself, a dissatisfied claimant may appeal to a local appeal tribunal, which usually sits in public. Legal representation is allowed, if the chairman consents for special reasons. Legal representation has been employed in about 2% of the cases heard,[1] but in many cases the claimant has the help of a non-legal but experienced representative of a trade union or other organisation.

Either the claimant or the insurance officer may appeal from the decision of a local tribunal to the Industrial Injuries Commissioner, a lawyer of experience and standing appointed by the Crown. The Commissioner is entitled to the help of one or more qualified assessors if in any case a factual question of special difficulty arises; this provision entitles him to call on medical advice. There is no appeal from the decision of the Commissioner.

Some of the Commissioner's decisions over the last twelve years have been published, and Mr. Neville D. Vandyk [2] has reviewed the 53 appeals between 1935 and 1958 which were based on medical evidence. 35 were claims for death benefit, 16 for injury benefit, and 2 for disablement benefit. Only 6 were decided in favour of the claimant.

What conclusions should be drawn from the fact that so few appeals were favourable to the claimant? In part, it may reflect sound judgment on the part of the local tribunals from whose decision the appeals were brought. But it may be because the onus of proof has been placed on the claimant. The Act of 1946 lays down certain presumptions in favour of the claimant. Where it is shown that an accident happened "in the course of employment", it is to be deemed also to have arisen "out of" it unless the contrary is proved, and in certain cases a disease is to be presumed to be due to the nature of the claimant's employment unless the contrary is proved. It is perhaps a fair inference that in all other matters Parliament intended the burden of proof to rest upon the claimant. At all events, it is the Commissioner's practice to require the claimant to show that the death or injury resulted from the accident.

A miner collapsed and died whilst digging up packing for pillars supporting the roof. He had been employed for three weeks on this job which was no more strenuous than his previous work as a stripper. Death was due to coronary occlusion. There was a conflict of medical opinions, and it was held that the claimant had not proved that the deceased's death was accelerated by the work he was doing. The Commissioner said that he was not entitled to allow the claim if the evidence proved no more than that it was possible, but not probable, that the work accelerated death. It was accepted that the deceased's effort at work would not have caused an increase in the demand for blood which the arteries could not supply; in the medical assessor's opinion normal work, however strenuous, does not cause or contribute to coronary occlusion, and death would have occurred when it did whatever the work the deceased was doing.[3]

That the same principle applies to the prescribed diseases is shown by the following case:

The cause of death of a mental nurse had been certified as hæmoptysis and sarcoidosis. Tuberculosis was one of the diseases prescribed in relation to his employment, and during the nine years before his death he had attended a chest hospital on various occasions. Medical opinion was divided on the connection between sarcoidosis and tuberculosis, and it was held that on the medical evidence available it had not been established that death was due to tuberculosis.[4]

1. Committee on Administrative Tribunals and Inquiries, 1957. Cmnd. 218, para. 173.
2. *Solicitors' J.* Dec. 9, 1960, p. 1012; also printed in the *Med.-leg. J. Lond.* 1960, **28**, part iv, p. 184.
3. R(I) 16/56.
4. R(I) 38/56.

In a claim for death benefit, it is necessary to show that death was caused by the accident or prescribed disease. In many cases the deceased already had the disease which proved fatal. In such cases it seems that the Commissioner will be satisfied if it is proved on a balance of probabilities that death was accelerated by the accident or prescribed disease. Put in other words, the question is—would this man have died when he did but for the accident or prescribed disease? This interpretation corresponds to that generally adopted by the law whenever it is necessary to consider questions of causation, and it will probably appeal to doctors as a common-sense and workmanlike test.

In some of these cases there was a considerable time-lag between the accident and death. A substantial time-lag will not necessarily rule out a claim for benefit, though it may make it more difficult to prove that death was due to the injury.

A miner injured his left shoulder by catching it against a steel bar. Over seven weeks later he was certified to be incapable of work by reason of arthritis of the left shoulder. Two months after the injury there was X-ray evidence of a bone lesion in the humerus, and within six months there were widespread metastases from a highly malignant sarcoma of bone. Death, fourteen months after the injury, was due to secondary deposits and toxæmia from a primary sarcoma of the humerus. The claim for death benefit was allowed.[5]

The burden of proof imposed on the claimant clearly calls for a high standard of medical evidence.

## Public Health

### Respiratory Infections

IN the week ended Jan. 7, deaths attributed to influenza numbered 150; the total for the previous week was 45, and for the corresponding week in 1960, 34. Many of these deaths took place in the Midland region, and, to a lesser extent, in the North Western region.

Features of the Birmingham outbreak, in which adults of working age seemed predominantly affected, were sudden onset with malaise, pyrexia, and profuse night-sweats. Some patients had sore throats; and most had a cough, pharyngeal congestion, and œdema of lymph-follicles on the posterior pharyngeal wall.

Vulnerable contacts appeared to escape infection; and there was little evidence of direct case-to-case infection in households. Some who had Asian influenza in the previous epidemic were again affected.

The epidemic in Birmingham is now subsiding, but possibly the opening of the schools will be followed by fresh infections, first among the schoolchildren and later among their parents.

### Diphtheria in Camberwell

Up to Tuesday last no further cases of diphtheria had been reported in Camberwell, where a child fell ill with diphtheria on Dec. 19 and subsequently 29 children were sent to hospital, 10 as clinical cases. Seven days had elapsed without a new case. Swabbing and re-swabbing is continuing.

### Death of Windscale Employee

An open verdict was recorded [6] on Jan. 16 at an inquest on a 58-year-old former employee of the United Kingdom Atomic Energy Authority who worked at the Windscale plant and who died on Dec. 30. A pathologist said that death was caused by cardiac failure due to chronic myeloid leukæmia. In 1957 the deceased had begun an action against the authority alleging that he had leukæmia contracted during his work and due to atomic radiation. The action had still to be heard.

5. R(I) 26/57.
6. *Times*, Jan. 17, 1961.

## In England Now

*A Running Commentary by Peripatetic Correspondents*

FINGER-NAILS on the menu again at Cockaignshire County Hall, where the executive council is hearing Mrs. A.'s complaints, or at least the first half-dozen or so, against Dr. X. for laches, incivism, and sheer downright ignorance when dealing with her obesity.

Four-foot-ten Mrs. A., who tips the scale at twenty-two stone and has no difficulty in making the weight, was getting the bad news from a British Railways weighing-machine she had discovered behind the 2nd-class refreshment rooms (where the porters hide when they hear a train coming) when she noticed that the instrument bore a chart giving average weights for height and age. Simple extrapolation of these data revealed that, with her weight and age, she should be eight feet tall, and she therefore claims to be in fact a dwarf and that Dr. X. should have treated her for vertical undergrowth rather than for circumferential overgrowth. Also the machine, in its death-throes, bequeathed to Mrs. A. a little card. On one side was printed her weight, followed by the interjection COR!; and on the other side it said she was born under the zodiacal sign Scorpio, was easily put-upon because of her trusting nature, lucky stone the carbuncle.

Mrs. A. told the council she had always had carbuncles and come to think of it Dr. X. hadn't been too clever about those either, simply telling her, more—or, rather less—diet, and it stood to reason little bits of food for a long time came to the same thing as lots of food for a short time, which was what *she* believed in, Nature's Way Was Best, no wonder she was always craving for chocolates if she should be eight feet high . . .

Furthermore (claimed Mrs. A.), she attended every surgery Dr. X. held, as well as calling him to her house several times a week, to enable him to keep in touch with her case, but he showed no real interest that was the trouble with Capricornians, no sympathetic planetary vibrations. Neither did his weighing-machine give out little cards, at least not to panel patients it didn't, but what could you expect from a doctor who announced that until the zodiacal significations could give him three in a row at Newmarket, a horoscope for him was what he looked down ears with . . .

Dr. X. said in reply that from the way his weighing-machine had got countersunk into the floor, he thought Mrs. A.'s sign should be Libra, lucky stone the gall-stone. He admitted failing to reduce her weight and invited suggestions for dealing with a woman whose usual elevenses consisted of a pound-and-a-half of chips and a bottle of invalid port, and who, because her pills were labelled " before meals ", always insisted on taking a meal after them. He added bitterly that he'd missed the big race at Kempton Park and whatever the Minister's, the Chairman's, the Clerk's, or Mrs. A.'s zodiacal signs might be, on this occasion Taurus was certainly in the ascendant . . .

Both parties then withdrew and the Chairman announced he was sure the stars foretold they'd be able to fine Dr. X. pretty heavily for something or other, if it was only that last crack, and at least it would help to pay for the damage Mrs. A. had done to the lift.

* * *

A good theatre sister resents her property being put to unconventional uses, so last summer when I wanted to borrow a Foley catheter I sneaked it from under sister's nose. There was a wasps' nest under one of the rafters outside my house and my family continually urged me " to do something about it ". The entrance was short and very narrow, and on two consecutive nights I tiptoed up a ladder as soon as dusk had fallen and tried to pour cyanide down the hole; but each time the little yellow and black devils awoke and, despite a muffler and gauntlets and trousers tucked into socks, I had to beat a hasty retreat stung in several places. On the third night I crept up softly, passed a well-lubricated Foley into the hole

and quickly blew up the 30 c.cm. bag, thus totally blocking the exit. Then at my leisure in went the cyanide; and honour, and my family, were satisfied.

• • •

Mrs. A: Oh yes, ever so nice he is. I always see the bald one with the moustache. Just been on his holidays he has. I've been coming here for the last 7 years for my psoriasis.

Mrs. B: Well, I've been coming here for the last 12 years, and I've never seen you before. I come for the ulcer on me leg, you know. I used to see old Dr. Black, but maybe you know him? Very nice he was. He said he had never seen anything like my leg. I think they will have to take me in again. Yes, I always come in about this time of year. My daughter and her husband have their holidays you see. My leg gets ever so much better when they take me in.

Mrs. A: Yes, I always says to my hubby, I says, they can do so much more for you in the hospital than your own doctor can. I mean he hasn't got the time, and he can't give you the stuff that the hospital can. Very rich the hospitals, you know, give you lovely ointment and bandages and all. My doctor only gives me a little bit of ointment, and then it's no good. The doctor here said he was going to send me back to me own doctor last time I came, but I wasn't having none of that. I told him straight. My husband paid his stamps, I said. Every week, I said. I was entitled to hospital treatment, I said. I wasn't going to let him treat me like that!

Mrs. B: I'll never forget the time they took me into hospital. Marvellous it was. The food was ever so good, and if it wasn't for that rubber sheet they make you lie on, I'd have had nothing to grumble about. They said they were going to operate on my leg last time, but nothing ever came of it. Only talk. After all the palaver, and X rays and all, they decides not to do it. Not that I'd have had an operation, mind you. They killed my old Dad in here, eighty-six he was—fine old man. Yes, he had an operation. No, I wouldn't let 'em touch me.

I listen to their chatter from behind the clinic door. What a fate. There seems little chance of referring these ladies back to their own doctor. Mrs. B will not see a surgeon, but will see me in three weeks' time (a month is too long), and a week later Mrs. A is in the corner bed on the ward. I suppose the customer is always right, and there is no doubt that our customers know exactly what they want.

• • •

While the chairman of the health committee and I were visiting one of our largest but least populated Hebridean Islands (density 500 acres per head) to look at—of all things—slaughterhouses and burial grounds, we heard of a family remarkable for its longevity. One of the menfolk was reputed " to have kept 180 Christmasses in his own house ". A niece, who is also buried there, has a tombstone which records her age as 128 years.

In due course we mentioned our discovery at a meeting of the health committee and it was suggested that the stone should not be allowed to weather away. Accordingly " it was unanimously agreed that the stone should be suitably protected and preserved ", even though some doubt persisted as to the truth of the claim. Indeed, one member summed it up neatly by describing the deceased as a " monumental liar ".

• • •

A WELLCOME REPLY

" Darken not ", you said, " our doors again.
From sending leaflets please refrain.
My dustbin's full, my fires are swamped
With piles of mail that you have dumped.
Joy can't for me be unconfined
Until to Hades you're consigned."

When you commanded, we obeyed,
No legate called, no mail prepaid
Was sent by us to bring you news
Of purges, pills, and wizard brews.
And now your children's plaintive cries
Reflected back from rain-washed skies,
" Our dad ain't got his Wellcome Diary ",
Have reached our ears in regions fiery.

Let Burroughs Wellcome be your friend,
Give them your name and where to send.
Let them restore your outlook bright,
O traveller in the realms of write.

# Letters to the Editor

## ACUTE INTUSSUSCEPTION IN CHILDHOOD

SIR,—Mr. Campbell Cooke and Dr. Lewis [1] quote me on multiple intussusception. Case 1 is the one they mention; and I include 2 others that I have seen.

CASE 1.—A girl aged eleven months was admitted to hospital on April 18, 1959, with attacks of screaming, and apparently severe abdominal pain of twelve hours' duration. The bowels had not moved during this time. No purgatives had been given. No mass could be felt abdominally or rectally. No blood was noted on the examining finger after rectal examination. Plain X-ray of the abdomen showed a number of fluid-levels in the small bowel. Laparotomy was carried out through a para-umbilical paramedian incision under general anæsthesia. 15 ileoileal intussusceptions were found in the small bowel. 1 was 4 in. long; 6 others were over 1 in. in length, and the rest were smaller. All were easily reduced. No predisposing cause was found, but it was noted that the whole small bowel was very active. The child made an uneventful recovery from the operation and was discharged in good health.

CASE 2.—A boy aged two years was admitted on May 6, 1959, after screaming and vomiting for six hours. He had also passed a stool intermixed with red mucus. A mass was found under the left costal margin. This was not palpable rectally; but red-tinged mucus was observed on the examining finger. At laparotomy an ileocæcal intussusception was found and easily reduced. The small bowel was then examined and found to contain 4 ileoileal intussusceptions each about 1 in. long. These, too, were easily reduced. Hyperperistalsis was present throughout the small bowel. This child also made a good recovery.

CASE 3.—A boy aged four months was admitted to hospital on May 15, 1959, having presented with a ten-hour history of intermittent screaming attacks, abdominal pain, and vomiting. His bowels had not moved in that time. A mass was felt under the right costal margin. At laparotomy an ileocæcal intussusception was found at the hepatic flexure. The small bowel was searched and 4 ileoileal intussusceptions were found. All the intussusceptions were easily reduced. The child made an uninterrupted recovery.

Aird [2] states that ileoileal intussusceptions may follow purgation. He instances a nineteen-month-old child described by Gill [3] who was found to have 6 or 7 ileo-ileal intussusceptions. He also states that transient self-reducing partial intussusceptions may be common in enteritis. In the 3 cases I describe there had been no purgation; and there was no evidence of enteritis. But in all 3 the small bowel was hyperactive, which presumably also occurs in purgation and enteritis. This state of hyperperistalsis coupled with localised spasm may, as Campbell Cooke and Lewis point out, initiate an intussusception.

It is interesting to speculate further on the fate in two instances of these small ileoileal intussusceptions. Firstly, in cases of ileocæcal intussusception where the small bowel is not examined at laparotomy, an ileoileal intussusception may propagate and produce symptoms that are wrongly referred to as recurrent intussusception. Secondly, attacks of abdominal colic which are so common in children and for which no cause is found may in fact be due to small ileoileal intussusceptions that reduce spontaneously.

My thanks are due to Mr. Stanley Lee and Mr. Henry Young, consultant surgeons to New Cross Hospital, Wolverhampton, for allowing me to treat and discuss their patients.

Leicester Royal Infirmary, Leicestershire. JAMES HADFIELD.

1. Campbell Cooke, D., Lewis, E. C. *Lancet*, 1960, ii, 1359.
2. Aird, I. Companion in Surgical Studies, p. 817. Edinburgh, 1957.
3. Gill, W. G. *Brit. J. Surg.* 1938, **25**, 707.

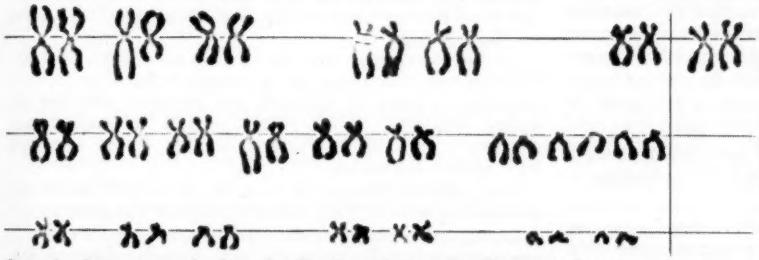
## TRANSLOCATION HETEROZYGOSITY IN MAN

SIR,—Recently a few chromosomal translocations (or presumable translocations) have been described in association with mongolism,[1–4] polydyspondylism,[5] and a variant of the Klinefelter syndrome.[6] All of them concern the acrocentric chromosomes of groups 13–15 and 21–22. It is believed that satellited chromosomes (such as nos. 13, 14, 21 and possibly 22 in man) are particularly predisposed to translocations at some point along the secondary constrictions.

We have now observed an individual with a translocation between the second chromosome and one of the chromosomes of group 6–12, both having submedian centromeres.

A normal female, born in 1943, has a pedigree showing an association between congenital auricular septal defect of the secundum type and chromosomal variations.[7 8] Her affected mother, born in 1906, is probably a 46/47 chromosome mosaic. The extra chromosome belongs morphologically to group 6–12. The karyotypes of the father, two brothers, and one sister, all unaffected, are as yet unknown. At a thorough examination (including electrocardiography and X-ray examination of the heart) in 1959 by one of us (P. Z.), no abnormalities were found.

The *cytogenetic analysis* was based on cell cultures from a skin biopsy taken on May 5, 1960. The chromosome number, as determined from 25 mitotic metaphases, was 46. 13 of these cells have been photographed and the chromosomes matched in the usual way. All of them displayed the karyotype shown in the figure. A large segment is missing from the long arm of one of the chromosomes of the second pair while one of the chromosomes of group 6–12 has a corresponding prolongation. According to the length of the short arm we have tentatively placed the latter chromosome at position 10. There is no evidence that the sex chromosomes are involved. The interpretation is that this individual is a translocation heterozygote. If extra chromosomes predispose to translocations and other irregularities of meiosis the alleged abnormal karyotype of the mother might have been a contributing factor in the origin of this translocation heterozygote.



**Somatic chromosomes in dermal-cell culture from patient interpreted as a translocation heterozygote. One chromosome (no. 2) is defective and the chromosome with the alleged translocated segment has been tentatively placed at position 10.**

One might speculate about the obstetric prognosis for this girl who is likely to produce egg cells half of which will have grossly unbalanced chromosome sets. The most likely consequence should be a high risk of zygotic or very early fœtal mortality which would be apparent only as reduced fertility.

Considering that reliable data on human cytogenetics are still very limited and that a few instances of translocations have already been found, it is possible that translocation heterozygotes, although exceptional, might not be insignificant in human populations. It remains to investigate to what extent such heterozygotes contribute to fœtal mortality and/or viable but defective offspring.

This investigation has been aided by a grant from the Swedish Atomic Research Council.

Institute for Medical Genetics,
University of Uppsala,
Sweden.

J. A. BÖÖK
BERTA SANTESSON
PER ZETTERQVIST.

1. Polani, P. E., Briggs, J. H., Ford, C. E., Clarke, C. M., Berg, J. M. *Lancet*, 1960, i, 721.
2. Penrose, L. S., Ellis, J. R., Delhanty, J. D. A. *ibid.* Aug. 20, 1960, p. 409.
3. Carter, C. O., Hamerton, J. L., Polani, P. E., Gunalp, A., Weller, S. D. V. *ibid.* Sept. 24, 1960, p. 678.
4. Fraccaro, M., Kaijser, K., Lindsten, J. *ibid.* 1960, i, 724.
5. Turpin, R., Lejeune, J., Lafourcade, J., Gautier, M. *C.R. Acad. Sci., Paris*, 1959, **248**, 3636.
6. Lejeune, J., Turpin, R., Decourt, J. *ibid.* 1960, **250**, 618.
7. Böök, J. A. *Acta soc. med. Upsal.* 1960, **65**, i.
8. Böök, J. A., Santesson, B., Zetterqvist, P. *Acta pædiat.* (in the press).

## LIFE AT HIGH ALTITUDES

SIR,—Your leader (Dec. 31) raises some interesting points.

What fixes the limits of hæmoglobin and red-cell levels in normal individuals? These levels remain remarkably constant for any one individual, considering the varied demands on erythropoiesis.

The hypoxic theory of erythropoietic stimulation is still current, although most workers probably accept that hypoxia acts through humoral factors. From this it is easy to imagine that excess of these humoral factors might result in polycythæmia.

By courtesy of Dr. Edward William, I have studied the levels of plasma erythropoietic hormone in 3 members of the 1960 Middlesex Hospital Physiological Expedition. Assay involves estimating the percentage mitoses of erythroid elements in the bone-marrow of rats injected with plasma, mitosis being arrested by colchicine after the injection at the stage of metaphase (data to be published).

The three individuals ascended rapidly by helicopter to 14,300 ft., and plasma-samples were taken on the 3rd and 19th days of exposure to these conditions.

The level of erythropoietic hormone, estimated as above, was not significantly raised on either of the two test-days; nor did the values differ greatly on the two days (normal mitotic index 3·8).

| | *3rd day at 14,300 ft.* | *19th day at 14,300 ft.* |
|---|---|---|
| R. E. .. .. .. .. | 6·2 | 4·0 |
| J. A. .. .. .. .. | 6·2 | 6·3 |
| C. Y. .. .. .. .. | 4·2 | 4·7 |

Hæmoglobin levels, on the other hand, rose progressively from London (taken as sea-level) till the 19th day at 14,300 ft.

| | *London (sea-level)* | *3rd day at 14,300 ft.* | *19th day at 14,300 ft.* |
|---|---|---|---|
| R. E. .. .. .. | 110% | 110% | 116% |
| J. A. .. .. .. | 96% | 98% | 110% |
| C. Y. .. .. .. | 98% | 111% | 121% |

Though these data are incomplete they suggest that the plasma-level of hormone is not increased in spite of the subjects becoming progressively polycythæmic. This accords well with Stohlman's animal work [1]: he found a maximum plasma-level after about 16 hours' hypoxia, which had fallen almost to normal after 48 hours. This could be explained by an increased removal-rate of hormone from plasma by a hyperplastic marrow. If correct, this favours the hypothesis that the hormone acts on two sites—the stem-cell, and the increased progeny of stem-cell stimulation.

Your concluding comments on an undefined link between hypoventilation, hypoxia, and polycythæmia are of great interest, but I prefer a different point of view. Why do some patients with hypoxia, with or without hypoventilation, develop polycythæmia and not others? I can, for instance, remember patients with chronic chest-disease, in ventilatory failure with hypercapnia and arterial $O_2$ unsaturation, who did not develop polycythæmia.

1. Stohlman, F., Jr. *Ann. N.Y. Acad. Sci.* 1959, **77**, 710.

In a three-year follow-up of an obese patient with the hypoventilation syndrome a raised hæmoglobin or packed-cell volume was never found. Red-cell mass measured by the $^{51}Cr$ labelling method was normal, yet the $pCO_2$ level was commonly above 60 mm. Hg, and arterial $O_2$ saturation was in the region of 75–85% for long periods. One random sample showed a high level of plasma erythropoietic hormone (mitotic index 9·5) in this patient.

These findings are difficult to interpret. Possibly a pituitary-hypothalamic lesion in patients with a hypoventilation syndrome is also responsible for the failure of polycythæmia to develop. This hypothesis finds some support in the observation of Stewart et al.[2] that hypophysectomised animals do not respond to anoxæmia by polycythæmia unless the stimulus is severe.

I wish to thank Prof. A. Kelwick for permission to publish data of a patient under his care.

Institute of Clinical Research,
Middlesex Hospital Medical School,
London, W.1. HILLAS SMITH.

## PULMONARY EMPHYSEMA

SIR,—Dr. Bass (Dec. 17) opens his criticism of our article [3] with the question: " They dismiss the lung as ' primarily an organ of motion '. How else can one visualise it? " Since our article from the title onwards is devoted to answering this very question, his opening statement is somewhat puzzling. That Dr. Bass did not miss our answer to this question is apparent in his subsequent critical comments about " visceral lung function ". Therefore his question can only mean that, despite our contentions, his conviction is that no answer is necessary or indeed possible. Yet in his letter Dr. Bass does not question any point in our discussions contending that an alternative concept of lung function and of emphysema is indeed necessary and possible.

Dr. Bass does not deny our contention that emphysema has remained an unsolved problem so long because prevailing belief of its mechanical origin based on the concept of the lungs as an organ of motion does not bear on the real problem; this is the missing link between structure and function in the lungs. Hence there is urgent need for an alternative concept.

He does not question the evidence of the autonomic activities of the structures involved in diffusion-surface creation which certainly justifies the assumption of " visceral lung function ", particularly since the primary function of the lungs is to afford diffusion surface for gas-exchange. The gist of his criticism is that visceral lung function fails to explain the origin of emphysema to his satisfaction, hence must remain a theory until additional evidence is provided. Already in our introduction we emphasised that ours is a theoretical concept offered as a new approach to the problem. We are satisfied to have it accepted as a working theory which, incomplete as it still is, affords reasonable explanations of many aspects of emphysema discussed in our article.

Dr. Bass gives considerable space to describing experimental production of emphysema by airway obstruction in rats' lungs. Such experiments have so many times proved futile in the past, we think, because they are without relevance to the problem of emphysema in man. We venture to predict that the solution of this problem will come from research on the activities of the structures involved in the regulation of the diffusion surface.

We wish to thank Dr. Bass for his letter drawing attention to our article, the main purpose of which was to arouse interest and so stimulate research to find the missing link of the nature of " visceral lung function ", which is the key to the problem of pulmonary emphysema.

New York. ISRAEL RAPPAPORT.

2. Stewart, G. E., Greep, R. O., Meyers, O. O. *Proc. Soc. exp. Biol., N.Y.* 1935, **33**, 112.
3. Rappaport, I., Mayer, E. *Lancet*, 1960, ii, 1217.

## TREATMENT OF DRUG ADDICTION

SIR,—In reply to Dr. Stungo's letter (Jan. 7) we have followed-up, and are following-up, all the patients we have treated.

Our experience has been that patients who relapse do so within days or weeks rather than months after withdrawal.

Those who did relapse—with 2 exceptions—six months after withdrawal, and after becoming established in a steady job, reported almost immediately, stated their reason or reasons for the relapse, and asked to be cured again. (" Cure " is the word they use.)

Only 1 patient in this series has relapsed and not returned for treatment. She was free from addiction for eighteen months, living in the country, but returned to London and went to live with an old friend—an addict.

Such success as we have achieved has been largely due to treating each patient as an individual. Briefly, this has meant gaining his confidence, understanding his particular difficulties (at the same time making it clear that we were not impressed by fantastic stories of disaster), and helping him to build up his self-respect and to acquire self-confidence.

In the early stages of treatment vitamins were given primarily for the malnutrition which was so often present. One ' Orovite ' tablet and ascorbic acid 250 mg. were given daily, and, though the dose of heroin and cocaine remained more or less unaltered, barbiturates were slowly cut down. Many complained of tiredness, in some patients due possibly to unaccustomed regular employment, and for this nicotinamide was found to be useful.

Intensive vitamin therapy was effective not only for the malnutrition from which many of the patients suffered but also for producing a sense of wellbeing and increased efficiency in dealing with jobs. These results, though less marked, are comparable with the results recorded in patients who had suffered from alcoholism.

Amiphenazole (' Daptazole ') was not given until the heroin or morphine was cut down, and at this stage it was given orally.

During the actual withdrawal treatment ' Parentrovite ', perphenazine, and promethazine were given by injection, the amount and frequency of each injection being determined by the patient's condition and his reaction to treatment.

After withdrawal was completed the patients continued to put on weight and to experience a sense of wellbeing, but it has become increasingly obvious that it is essential to continue to give orovite, ascorbic acid, and nicotinamide (250 mg.) for some months.

Preliminary therapy cut down the need for lengthy withdrawal treatment and therefore the cost of nursing-home fees and private nurses. Fees presented no problem to private patients. I charged no professional fees to the many patients who were referred to me and who obviously needed the money to make an effort to improve social and economic standards and to pay off their debts. Consequently, when they had settled down to regular employment they were able to save money towards the cost of their nursing-home treatment. Borrowing was not encouraged but at the same time every effort was made to help them to clear up their previous debts before beginning withdrawal treatment.

In his group 3 Dr. Stungo includes a certain proportion of people associated with the world of entertainment and goes on to state " they rarely have any incentive to attempt a cure and are mostly immature psychopaths who lead degraded lives ...".

In our series of patients we have 8 professional musicians and of this number only 1 could be classified as a psychopath who leads a degraded life. He is still under treatment and in a job, but despite the fact that he has reduced his intake of heroin and barbiturates it is doubtful if he will ever be clear of his dependence on drugs. 2 of these musicians have been clear of dependence on drugs for over eight months, 2 for four months, and 1 for two months. 2 who were on large doses of heroin and cocaine, and who were becoming hallucinated, have been reduced to small doses which are slowly being cut down.

Our experience of those addicts who have served prison sentences has been that they have relapsed almost immediately after release.

Our experience of addicts reporting for treatment has been that they minimise the amount of drugs they are taking and that they continue for a short time to augment supplies from the black market. After a period varying from a few days to a few weeks they realise that it is possible to cut out illegal supplies and adjust to such legitimate supplies as will be provided during the period of stabilisation. During this period of stabilisation intensive psychotherapy helps the patient to acquire enough insight into his condition to enable him to cooperate in his treatment, to face the idea of regular employment and a more normal way of life, and finally to avoid the temptation to augment his income by selling drugs.

I used the term " clear of dependence on alcohol " in a brief paper on the treatment of alcoholism in 1954, in which no claim was put forward for a cure of alcoholism because it was not possible to state that those patients would not at some future date revert to alcohol. I am still not prepared to put forward any claim for " cure " of my alcoholic patients although over 80% of over 100 patients treated have been clear of dependence on alcohol for five years, and the majority for six or seven years or longer.

Therefore the term " clear of dependence on drugs " was used, but it was not meant to imply a " purely temporary state of affairs ".

London, W.1. I. M. FRANKAU.

## NOT FOR SALE

SIR,—I am surprised that, in your leader last week, you agree so readily with the Under-secretary of State that " queue-jumping for hospital beds " is not a matter that can be analysed statistically by lay administrators. Surely all that is required is information with regard to the interval between the consultation and the date of admission, and whether the former was a private or a hospital consultation. Patients could be asked to give this information when their admission was being arranged.

If we were then to compare these figures for such operations as tonsillectomy, hæmorrhoidectomy, herniorrhaphy, &c., we could readily refute or confirm the existence of this alleged " racket ".

Public Health and School Medical Department, Oldbury. H. TABBUSH Medical Officer of Health.

## ORAL POTASSIUM SALTS

SIR,—There have been several recent references in your columns to the effervescent tablet of potassium citrate which I have formulated, and I should like to draw attention to a number of precautions which should be observed in their manufacture and dispensing.

The tablets are very susceptible to moisture and deteriorate rapidly if exposed to moist conditions. In the course of manufacture, precautions should be taken to prevent the uptake of moisture during compression and packing. The finished tablets should be issued in containers which hold not more than 1000 and which contain a drying agent to prevent moisture from being absorbed during storage. The tablets should be dispensed in well-closed containers, preferably with a drying agent to keep the tablets dry during use by the patient. If these precautions are stringently observed, a satisfactory preparation will be obtained.

It is possible that some modifications of the formula, at present under investigation, may result in a preparation which is easier to compress on a large scale. A number of manufacturers have shown interest in producing a suitable effervescent tablet but, in the meantime, it may be of interest to your readers to know that Samoore Ltd. (Lawrence Road, London, N.15) are now able to supply tablets according to my formula.

Royal Free Hospital, London, W.C.1. J. W. HADGRAFT.

## SPINAL INJURIES

SIR,—Much in Mr. Roaf's article of Jan. 14 is, as he himself points out, accepted all over the world, since Guttmann in 1944 (not 1947) introduced the clinical application of neurophysiology into the treatment of cord injuries. Guttmann showed to all willing to learn that the overstressing of the mechanistic theory in the treatment of fracture dislocation of the spine with cord or cauda-equina involvement often met with disastrous results.

Mr. Roaf claims that, since Guttmann's paper of 1947, there have been several recent advances in the management of spinal injuries with paraplegia.

Firstly, the " fundamental concept " of unstable rotational fracture dislocations as described by Holdsworth and investigated further by himself. This perpetuates the old misconception that radiological, experimental, or postmortem studies on vertebræ or ligaments can give a true picture of what really happens to the spine, as well as to the cord, at the time of impact in the living person. Do vascular damage and sudden disruptive muscle contraction count for nothing?

Secondly, he propagates open reduction and plating for the " unstable " fracture dislocation. Guttmann has repeatedly shown that conservative X-ray-controlled postural reduction in fracture and fracture dislocation achieves excellent results, with regard to both reduction of the spine and neurological recovery, in almost every case. Why does Mr. Roaf not mention this fact? Are we to see still more cases of failed open reduction, surgically produced deformity and infection, painful stiff backs, and imperilled neurological recovery?

Thirdly, the peripheral operations which he mentions for the treatment of spasticity are, with the exception of iliopsoas myotomy, nearly as old as orthopædics itself. (Achilles-tendon tenotomy has long been replaced by the far more effective tendon lengthening.)

National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury, Bucks. L. S. MICHAELIS.

SIR,—Having read Mr. Roaf's article and having spent the past 13 years dealing with paraplegic patients, mostly traumatic lesions, I should like to comment on certain points.

Firstly, his statement that Guttmann " ignored the spinal displacement " and " avoided reduction " is quite untrue. Guttmann's publications (his monograph in the *Official Medical History of the War* [1953] and other papers,[1 2] and more recently his chapter in *Modern Trends and Diseases of the Vertebral Column* [1959]) all stress the necessity for reduction of the displaced spine in both stable and unstable fracture-dislocations. What he does avoid and indeed rejects as unnecessary and even harmful is open reduction and fixation by wire and, in particular, metal plates. He has proved that in the vast majority of these patients the spinal displacement can be safely and effectively corrected by his method of postural reduction.

Mr. Roaf puts his finger on the key-point of a very important problem when he says " . . . the major part of the damage to the spinal cord is done at the moment of injury ", and again he stresses, quite rightly, that in some of the successes claimed for laminectomy the cord would probably have recovered anyway. The same, of course, applies to so-called decompression of the cord by open reduction and fixation with metal plates. His view that the latter is the modern treatment for unstable fracture-dislocation is not accepted by experienced workers in this field, including many orthopædic surgeons, both in this country and abroad.

1. *Proc. R. Soc. Med.* 1954, **47**, 1099, 1103.
2. *Practitioner*, 1956, **176**, 157.

In recommending intrathecal injection of phenol as the method of choice in treating spasticity, if the bladder is paralysed, he does not take into account the fact that a well-trained, automatic bladder in such cases is a strong contra-indication either to phenol or the longer established intrathecal alcohol injection.

Finally, in his reference to the treatment of intestinal ileus in tetraplegia, Mr. Roaf omitted to mention the most important measure in quickly overcoming a neurogenic ileus—namely, intramuscular neostigime.

National Spinal Injuries Centre,
Stoke Mandeville Hospital,
Aylesbury, Bucks. J. J. WALSH.

## PROPRIETARY NAMES OF DRUGS

SIR,—Many who already complain of the multiplicity of proprietary names of preparations of the same drug by different pharmaceutical firms will be disturbed to learn that yet again a single firm (Squibb) has recently marketed a new phenothiazine tranquilliser (fluphenazine dihydrochloride) under different names in the United States of America (' Prolixin '), in the United Kingdom (' Moditen '), and in Eire (' Anatensil ').

This practice is most undesirable because reports in the American literature of controlled therapeutic trials [1] or of side-effects (which are likely to be numerous, as with all phenothiazines) which refer to the drug by its American name will not be connected by most readers with the preparation under its proprietary name here.

Department of Therapeutics and Pharmacology,
Queen's University of Belfast. O. L. WADE.

## TREATMENT OF RESPIRATORY PARALYSIS IN SMALL CHILDREN

SIR,—I was very interested in the excellent paper of Dr. Powell and Dr. Smith (Dec. 3) and would like to add a few observations from my own experience with poliomyelitic children.

Since 1950 poliomyelitis has occurred in Israel. Experience had to be rapidly acquired, especially in treating infants, who still constitute about 80% of paralytic poliomyelitis victims in our country.

As many as 15% of the children in hospital might be in respirators at any one time. In the second half of 1953, 24 of 157 patients, 77% of whom were under the age of 2, required respirator treatment. In the following years we treated an average of 250 children a year (except in the years 1957, 1959, and 1960 when poliomyelitis was at a low ebb) of whom approximately 10% needed respirators.

We used chiefly the Drinker tank apparatus and a German model (the Schweinfurt) with a transparent glass cover, which allowed us to observe the child at all times.

The indications for use we learnt from experience. The right moment was when we began *to consider using a respirator*, in other words we should not wait until the general condition had deteriorated or until cyanosis had appeared.

Only those children with respiratory difficulties—the so-called " dry type " (Lassen)—were put in respirators. As soon as secretion increased (the " wet type ") we were forced to remove them and proceed with intermittent positive-pressure respiration. We finally adopted this method as the treatment of choice in all cases in which increasing secretion was a problem, since we observed that these cases were becoming more and more frequent.

The disease runs its course even in the respirator, and further paralysis and development of contractures may necessitate a change of treatment.

The rhythmic noise of the machine often lulls the physician and attendants into a false sense of security, and the child may suffer from lack of attention and from insidiously developing complications.

1. *Dis. Nerv. Syst.* 1960, **21**, 467.

To gain personal experience of the iron lung I spent approximately half an hour in one under the same conditions as our patients. There was an uncomfortable feeling of pressure around the neck; pressure on the chest was just bearable, although considerable and decidedly unpleasant. Coughing was not possible from the outset, and every attempt to talk required physical effort. The collar was too tightly applied, but the machine did not feel hermetically sealed, although the manometric pressure was correct at 15 to 20 mm. Hg.

Sometimes " weaning " children from the iron lung was difficult; in time they get so used to it that a state of symbiosis develops. When the respirator was removed some of them reacted strongly by grimacing, deterioration of breathing, weeping, &c. The rhythmic noise of the machine appears to be a factor and we therefore tried the simple expedient of leaving on the motor but nullifying its effectiveness by opening the small window in the machine. If the child's condition continued satisfactory with independent breathing it was time to remove him from the respirator.

The longest time spent in the respirator was 4 months.

Department of Pædiatrics,
Tel-Hashomer Government Hospital,
Israel. Y. ROTEM.

## DOES BUERGER'S DISEASE EXIST?

SIR,—I was encouraged by Professor Dible's letter of Nov. 19 to write out the following personal case-history which might help your readers to decide whether Buerger's disease exists or not.

The first indication that all was not well with my cardiovascular system was at the age of 31 years when I was serving as a medical specialist in the R.A.F. in 1946. The sudden spontaneous thrombosis of a large varicocele of the left testis—a rare complication of varicocele simulating an acute epididymoorchitis—led to three weeks' complete bed rest in hospital and numerous tests, all of which were negative. During this period of enforced rest I noticed tender areas in both calves. Subsequent convalescence was uneventful.

For the next ten years I had no further symptoms apart from spontaneous superficial venous thromboses with painful tender reddening of the skin in legs and forearms. These appeared at irregular intervals and each lasted a few days. Medical advice was finally sought in 1956 six months after severe cramping pains in the sole of the left foot set in. The pain was never experienced in the calf; it came on during brisk walking and was relieved by rest. I was regularly smoking 4 oz. of pipe tobacco a week in addition to three to six miniature cigars daily during the six months of claudication. This became steadily worse, eventually compelling rest periods after walking less than 100 yards.

I noticed coldness and numbness of the left foot, which was shiny and red after standing, especially the toes. Capillary filling was delayed and the left foot blanched on elevation. Nail growth became abnormal and the hairs on the toes of the left foot disappeared, as did the dorsalis pedis and posterior tibial artery pulses, the right foot being entirely normal. A paronychial infection of the left great toe gave rise to an indolent small ulcer which caused severe and relentless pain which prevented sleep. In addition night cramps in the left foot and calf were frequent until effectively controlled by quinine sulphate gr. 5. Meanwhile areas of thrombophlebitis migrans were practically always present in arms or legs, and when examined by a colleague several typical lesions were present. On the above history and physical findings, which included diminished appreciation to painful stimuli and light touch in the left foot, as well as fungus infection of both feet, a diagnosis of Buerger's disease was made; smoking was stopped at once and I was admitted to Hammersmith Hospital for six weeks. A biopsy of a superficial thrombosed vein of the right foot was reported as showing the appearances typical of thrombophlebitis migrans as seen in Buerger's disease. Left sympathectomy was advised by several colleagues but refused by my medical adviser and myself. Blood-pressure and electrocardiograms were normal, as were many other investigations.

After four weeks' bed rest and phenoxybenzamine ('Dibenylene') 60 mg. a day, rest pain disappeared and the ulcer healed. Fungus infection yielded rapidly to daily applications of Castellani's paint. For the next twelve months there was steady symptomatic improvement; superficial thrombophlebitis was only occasional; sole pain on walking was tolerable and could be "walked through"; nail growth improved and hairs began to appear on the toes. I was able to play squash, but was unfortunate in so doing to rupture a plantaris tendon or fibres of the soleus. This resulted in pain and swelling of the left leg with deep venous thrombosis, necessitating readmission to hospital. Anticoagulant therapy was begun and maintained for the next twelve months. Recovery was uneventful, and in the past three years there have been no further symptoms in the left foot. Although the pulses of the left foot are absent, blood-supply is good with normal nail and hair growth and normal capillary filling. All sole pain on exercise has disappeared and there has been no recurrence of superficial thrombophlebitis.

The disease process (dare I call it Buerger's?) appears to be completely arrested, and the grossly impaired blood-supply to the left foot is now apparently normal—presumably due to an efficient collateral circulation or to recanalisation of thromboses in smaller arteries. Fungus infection of the feet—surely a consequence and not the cause of ischæmia—has never recurred.

I wish to emphasise in this case-history the long period of thrombophlebitis migrans ushered in by spontaneous varicocele thrombosis ten years before the appearance of claudication and other ischæmic symptoms. Also to stress that claudication was confined to the sole of the foot. This symptom, which I have seen in three other young patients with histories of thrombophlebitis and ischæmia comparable to my own, was in one originally thought to be due to "fallen arches", the patient being referred to me from the orthopædic department. Sole pain on exercise—rarely seen in older subjects in my experience unless accompanied by severe calf pain—is in keeping with the widely accepted view that in Buerger's disease the smaller arteries are principally involved.

Bedford. DAVID LEWES.

## PROGNOSIS AND ANTICOAGULANT PROPHYLAXIS AFTER CORONARY OCCLUSION

SIR,—Dr. Byron Evans (Nov. 26) is certainly rendering a great service to both physicians and patients by reminding us how often treatment is given not so much because of an inner conviction as to its usefulness or indeed necessity but in order to soothe the prescriber's conscience or, perhaps more precisely, to still a feeling of guilt arising from his impotence in the face of a not fully understood yet serious condition. The case of long-term anticoagulants in myocardial infarction is very much to the point and, having the somewhat unpleasant experience of being a patient as well as prescribing it for my own patients, I am able to look at the problem from "both sides of the counterpane", as it were.

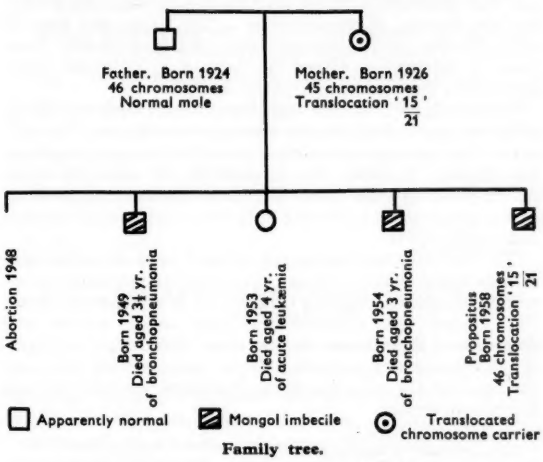
Surely, we are now in a difficult position. The M.R.C. report almost obliged us to give anticoagulants for fear that we might be thought failing in our duties if we withheld them. Now, Professor McMichael tends to confirm what some of us have suspected for some time—namely, that the benefits are at best marginal.

There is, however, yet another side to the picture. I have little doubt that long-term anticoagulants are in two respects harmful to the patient, quite independent from their pharmacological action. Firstly, they may engender in the patient a false sense of security which we now know to be unwarranted and thereby distract his attention from possibly more important actions (e.g., weight reduction); and secondly, their frequent and of necessity quite precise exhibition together with the necessary blood-tests, &c., tend to produce a "cardiac neurosis" in many sufferers and the desirability of this is, at least, doubtful. Is this not perhaps too high a price to pay for the rather spurious peace of mind of the physician?

Abertillery. K. TRIGER.

## MONGOLISM AND LEUKÆMIA IN THE SAME SIBSHIP

SIR,—Cytogenetic investigations have shown that mongolism is associated with an abnormal karyotype. In most instances the chromosome count is 47 and these mongols are generally believed to be trisomic for autosome 21 (Denver classification).[1–3] But there is a small group of mongols, clinically indistinguishable from the others, who have 46 chromosomes; analysis shows an abnormal chromo-




Family tree.

some resulting from a translocation involving one autosome 21 and another acrocentric chromosome.[4–7] The formation of this abnormal chromosome involves the loss of some material from both chromosomes, but individuals with such a translocated chromosome can be regarded as being effectively trisomic for autosome 21. In several cases investigation of the parents of these mongols has shown that one of the parents carries the translocated chromosome.[5–7] In two cases where more than one mongol occurred in the sibship, the mother and maternal grandmother had only 45 chromosomes, including the translocated chromosome.[6 7] We report here our findings in a further family in which there were three mongol sibs.

The details of the sibship are given in the figure. The propositus was a typical mongol imbecile, the third in the family, the two others having died in childhood of bronchopneumonia. The data on the mother's sibs are incomplete, but she is known to have been the last child in a sibship of either 7 or 8, and at her birth her father was 47 years old and her mother 43.

Chromosome counts and analyses were made from preparations of skin cells by the method of Harnden [8] and from preparations of white blood-cells by the method of Moorhead et al.[9] The counts are given in the table.

1. Lejeune, J., Gautier, M., Turpin, R. *C.R. Acad. Sci., Paris*, 1959, **248**, 1721.
2. Lejeune, J., Turpin, R., Gautier, M. *Ann. Génét.* 1959, **1**, 41.
3. Jacobs, P. A., Baikie, A. G., Court-Brown, W. M., Strong, J. A. *Lancet*, 1959, i, 710.
4. Polani, P. E., Briggs, J. H., Ford, C. E., Clarke, C. M., Berg, J. M. *ibid.* 1960, i, 721.
5. Fraccaro, M., Kaijser, K., Lindsten, J. *ibid.* p. 724.
6. Penrose, L. S., Ellis, J. R., Delhanty, J. D. A. *ibid.* 1960, ii, 409.
7. Carter, C. O., Hamerton, J. L., Polani, P. E., Gunalp, A., Weller, S. D. V. *ibid.* p. 678.
8. Harnden, D. G. *Brit. J. exp. Path.* 1960, **41**, 31.
9. Moorhead, P. S., Nowell, P. C., Mellman, W. J., Battips, D. M., Hungerford, D. A. *Exp. Cell Res.* 1960, **20**, 613.

CHROMOSOME COUNTS

| — | Tissue | Diploid no. | Chromosome counts | | | | Total cells counted |
|---|---|---|---|---|---|---|---|
| | | | <45 | 45 | 46 | 47 | |
| Propositus .. | Skin | 46 | 1 | 4 | 24 | .. | 29 |
| Father .. | Skin | 46 | .. | 2 | 20 | .. | 22 |
| | Blood | 46 | .. | 1 | 30 | .. | 31 |
| Mother .. | Skin | 45 | 3 | 25 | .. | .. | 28 |
| | Blood | 45 | 1 | 42 | 1 | .. | 44 |

The father of the propositus had 46 chromosomes indistinguishable from those of a normal male, while the mother had only 45 chromosomes. She lacked a chromosome in group 13–15, and also one in group 21–22. An additional submetacentric chromosome was present in group 7–12, and this was presumed to be the product of a translocation involving the missing 2 chromosomes. The propositus had 46 chromosomes, his autosomes being indistinguishable from those of his mother, except that he had an additional small acrocentric chromosome in group 21–22.

The evidence from this family and others reported so far indicates that while the presence of such a translocated chromosome does not appear to affect the individual carrying it, it considerably increases the probability of non-disjunction during gametogenesis. This is probably because the presence of the abnormal chromosome interferes with meiotic pairing and crossing-over.

The one child who apparently showed none of the features of mongolism died at the age of 4 years of influenzal pneumonia, lymphatic leukæmia being noted as a secondary cause. The clinical and hæmatological data amply confirm the diagnosis of acute leukæmia. In view of the high incidence of leukæmia among mongols,[10–12] the occurrence of these two conditions in the same sibship may be due to factors other than the play of chance.

Medical Research Council, Clinical Effects of Radiation Research Unit, Western General Hospital, Edinburgh, 4. KARIN E. BUCKTON
D. G. HARNDEN
A. G. BAIKIE.

Hortham Hospital, Almondsbury, Bristol. GRACE E. WOODS.

## A WATCHSPRING PESSARY RETAINED FOR 62 YEARS

SIR,—In view of the recent correspondence on gynæcological " records " (Nov. 26 and Dec. 10) you may be interested in the following case.

A married woman of 93 was admitted to the geriatric unit of this hospital (under the care of Dr. Trevor Howell) on Dec. 16, 1960, complaining of alternating diarrhœa and constipation for three weeks. She also had frequency of micturition, dysuria, pain in the left loin, groin, and thigh, and suprapubic pain after urinating. She was found to have retention of urine and was catheterised. On rectal examination a mass was felt anteriorly. Vaginal examination revealed a mass, which, on viewing with a speculum, proved to be a pessary. This could not be removed at the time, and later Mr. Arthur Clift, consultant gynæcologist to Mayday Hospital, removed an impacted pus-covered watch-spring pessary and noted only a little inflammatory change in the vaginal wall. The pessary was swollen, soft, black, and rotted and was 2in. in diameter. The patient denied all knowledge of its presence.

She was married in June, 1888, and her son was born on Dec. 29, 1888. Nine and a half years later a ring was inserted at the Women's Hospital, Waterloo Road. Her husband was 44 years old at the time, and died in 1929 (aged 75) of carcinoma of the bladder. Thus the date of insertion of the pessary was 1898. Intercourse did not take place after that time. No further examination or change of pessary was conducted since that date. Surprisingly there had been no obvious discharge per vaginam over the 62 years that the ring had been in place.

Scanty hyaline and granular casts, epithelial cells, 90 mg. per 100 ml. protein, and occasional red and white cells were found in the urine. Vaginal swab culture grew enterococci, and occasional epithelial, red, and white cells were seen on wet film. The patient is now symptom-free and will return soon to her room at a home.

It is interesting to note that the date of insertion of the pessary was one year before the outbreak of the Boer War. This case serves as a reminder that adequate examination of the elderly female patient on occasion reveals a pessary which being " out of sight, out of mind " has been forgotten.

Queen's Hospital, Croydon. J. G. PRITCHARD.

## EXTERNAL CARDIAC MASSAGE

SIR,—Mr. Molloy is to be congratulated on his success in restarting ordered cardiac contraction by so-called " external cardiac massage " (Jan. 7), a term which you, Sir, in your recent editorial [1] condemned, and which in his case may not have had its traditional meaning.

Intermittent compression of the chest will increase the pressure in all intrathoracic viscera more or less simultaneously. If the intra-aortic pressure increase is of the same order as the intraventricular, a propensity of the heart passively to act as a " unidirectional pump " cannot initiate unidirectional flow. This can only result from an adequate pressure-difference between ventricles and large vessels; this is why manual compression of the heart is effective.

For anatomical reasons in this method of cardiac stimulation the effect on the left ventricle is relatively indirect; and the success of so-called " external cardiac massage " may well be obtained for the same reasons as when a misbehaving heart is given a gentle flick of the finger at thoracotomy.

St. Bartholomew's Hospital, London, E.C.1. F. E. WEALE.

SIR,—Dr. Molloy's letter (Jan. 7) invites comment on 3 points.

First he says, " This is to report the *successful use* of external cardiac massage, believed to be the *first case reported in this country*." As the patient died the next day it does not appear to me to have been very successful.

In 1957 Dr. J. Bullough and I [2] described 8 cases, all children, who survived our method of cardiac massage without thoracotomy; and I have since reported on an adult similarly resuscitated.[3]

The patient treated by Dr. Molloy should, I believe, have had a thoracotomy.

London, W.1. E. H. RAINER.

## ASYMPTOMATIC PARATHYROIDISM

SIR,—The paper by Dr. McGeown and Dr. Field [4] on neonatal tetany in a baby born to a mother with hyperparathyroidism provides additional valuable clinical data on this rare occurrence. They record the second instance in which a symptom-free mother of a baby with tetany was found to have a parathyroid adenoma, the first being the case reported from this laboratory in 1954.[5]

Questioned subsequently, the mother of our patient remembered having had occasional polyuria, and losing weight. But when admitted to hospital, she had no specific complaints; and the diagnosis was suspected, as in Dr. McGeown and Dr. Field's patient, entirely because of the tetany in her infants.

10. Carter, C. O. *Brit. med. J.* 1956, ii, 993.
11. Carter, C. O. *J. ment. Defic. Res.* 1958, **2**, 64.
12. Stewart, A., Webb, J., Hewitt, D. *Brit. med. J.* 1958, ii, 1495.

1. *Lancet*, 1960, ii, 1333.
2. Rainer, E. H., Bullough, J. *Brit. med. J.* 1957, ii, 1024.
3. Rainer, E. H. *ibid.* 1960, ii, 1880.
4. McGeown, M. G., Field, C. M. B. *Lancet*, 1960, ii, 1268.
5. Walton, R. L. *Pediatrics*, 1954, **13**, 227.

Perhaps it could be said that neonatal tetany in the offspring is a more sensitive indicator of maternal hyperparathyroidism than the more overt symptoms of renal colic, flank pains, &c. This is also suggested by the case of VanArsdel,[6] in which 3 years elapsed between the development of neonatal tetany in the infant, and the passage of the first renal calculus by the mother.

Department of Pediatrics,
State University of New York,
New York.

LYTT I. GARDNER.

## REABLEMENT AFTER A STROKE

SIR,—Your annotation of Dec. 31 speaks of this as a "considerable problem". May I draw attention to a book [7] in which a highly intelligent patient describes his experience and offers some solutions?

Douglas Ritchie, who will long be remembered for his "Colonel Britain" broadcasts during the war, was Director of Public Relations at the B.B.C. when, at 50 years of age, he suffered a cerebrovascular disaster. He tells with complete honesty his reactions to his doctors, nurses, physiotherapists, speech therapists, and friends—some of which would have surprised those who evoked them. Bereft of speech (on which his livelihood largely depended) he was faced with physical suffering, loss of mobility and independence, and repeated psychological trauma from frustration, fears of insanity, and sombre thoughts about the future. Yet, despite depression holding him frequently and for long periods, there is no hint of self-pity in the book: it is a statement of subjective fact.

Those of us who from time to time have the professional care of victims of this form of disaster know that our powers to bring about recovery are very limited. Rarely, if ever, do we consider whether the patient is wondering why he cannot be cured of his affliction as readily as he can of pneumonia or a broken leg, though the process may take a little longer. It took Ritchie many months to understand his situation and to realise that whatever was possible depended fundamentally on the efforts that he himself could initiate, maintain, and develop.

I found a lesson on every page of this book, the value of which extends beyond the victims of strokes to spastics and others who have suffered intracranial disasters but can still understand the written word.

London, W.C.2. ROCHESTER BERKLEY.

## MORTALITY DUE TO BLOOD-TRANSFUSIONS

SIR,—The mathematical error in Dr. Harris Joseph's letter [8] is unimportant; but even the lower figure of 1 transfusion death in 25,000 transfusions is so at variance with clinical experience that we American pathologists trust the validity of the Bureau of Vital Statistics' tally as little as its equally challengeable calculations of the incidence of penicillin deaths. The reason is the same. Deaths which might reasonably be attributed to penicillin are often ascribed to the condition for which the drug is administered; the patient would have recovered if he had not been killed by a penicillin reaction.

I myself have seen *at least* 10 transfusion deaths each year over the past ten years.[9] I admit that the diagnosis of cause is my own, but it is based on long experience of hæmatological practice. Even if the other 6000 or so pathologists in this country have each seen only 1 fatal instance a year of the pouring in of blood, for cosmetic, forensic, or other unscientific reasons, or to add an item to the patient's chart while failing to take into account the presence, even before transfusion, of an overloaded circulation, that would give a figure of 1 fatality for every thousand transfusions.

I remain convinced that one-tenth of 1% is still too low and not the real figure; and that blood-transfusion as practised here is a prominent cause, along with penicillin and the cytotoxic drugs, of unnecessary iatrogenic death.

Harlem Hospital,
New York City Department of Hospitals. ROBERT D. BARNARD.

## TREATMENT OF TENSION PNEUMOTHORAX

SIR,—I am glad to hear that Dr. Foster-Carter (Dec. 10) agrees with my views on the treatment of tension pneumothorax. He should not be surprised, however, to find that his needle is still used to decompress the pleura in these cases as, after all, it is still advertised in the Down Bros. catalogue. It is now fitted with a "flexible polyvinyl shield" which surely lends it an air of modernity.

I hope that Dr. Foster-Carter's voice from the past will result in the final abandonment of his apparatus.

St. Helier Hospital,
Carshalton. A. M. MACARTHUR.

## ORAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H.P.P./1

SIR,—If Dr. Smith cares to read our original article on H.P.P./1 therapy,[1] he will find the answer to his query (Jan. 7) whether we would be prepared to treat non-anæmic cases of subacute combined degeneration of the cord with our $B_{12}$-peptide complex. In it he will find a description of such a case—and its treatment.

F. S. MOONEY
J. G. HEATHCOTE.

St. Helens Hospital,
Lancashire.

## TOXÆMIA AND MEGALOBLASTIC ANÆMIA IN PREGNANCY

SIR,—Some four years ago I conducted a survey of anæmia of pregnancy in the native population of Fiji. It has been found impossible to complete the study, but the results obtained are of interest.

The population consists of indigenous Fijians, who are of Melanesian stock, and Indians, who are descendants of labourers indentured to work in the sugar-cane plantations about the turn of the century. The Indian population has retained its identity, customs, dress, and diet.

In all, 297 women were followed through pregnancy, 77 being Fijian and the rest Indian. Of this number, 49 had anæmia severe enough to warrant admission to hospital, and of these only 1 was Fijian. In all these cases bone-marrow aspiration was performed and the response to drugs noted. The anæmia was classified on the appearances of the bone-marrow as normoblastic or megaloblastic, and the diagnosis of toxæmia was made on the findings of blood-pressure, œdema, and albuminuria. In the 38 cases where there was sufficient information to warrant inclusion, the following results were obtained:

| | *Toxæmic* | *Not toxæmic* |
|---|---|---|
| Megaloblastic anæmia .. .. .. .. | 11 | 10 |
| Normoblastic anæmia .. | 0 | 17 |

$\chi^2$ test: $0{\cdot}005 > P > 0{\cdot}001$

There appears to be a significant correlation between megaloblastic anæmia and toxæmia of pregnancy.

As all cases of megaloblastic anæmia showed only a slight and transient response to vitamin $B_{12}$, but a satisfactory improvement with folic acid, it is possible that a dietary deficiency of folic acid was the precipitating cause of the anæmia. The Indian diet consists mainly of rice and curry, supplemented by a little of the local vegetables, but very little meat. Absorption is probably further decreased by almost universal intestinal parasites. On the inadequate data available, no correlation between the type of anæmia and diet or incidence of intestinal parasites was possible.

Megaloblastic anæmia was not seen in men or in non-pregnant women, but it is not clear whether pregnancy exhausted the already depleted stores of folic acid, or whether another process was active. Against the former was the high incidence of megaloblastic anæmia in primiparæ. Normoblastic

6. VanArsdel, P. P., Jr. *J. clin. Endocrin.* 1955, **15**, 680.
7. Stroke. By DOUGLAS RITCHIE. London: Faber. 1960. Pp. 174. 12*s.* 6*d.*
8. Joseph, J. H. *Lancet*, 1960, ii, 709.
9. Barnard, R. D. *N.Y. St. J. Med.* 1951, **51**, 2399; *ibid.* 1952, **52**, 1283.

1. *Lancet*, 1958, i, 982.

anæmia, which responded to iron, tended to be more common in multiparæ, although the numbers were too small to show a statistically significant difference. In all cases where the megaloblastic anæmia was accompanied by toxæmia, the toxæmia cleared when folic acid was given. Unfortunately, in this small series, there were no cases of normoblastic anæmia accompanied by toxæmia to act as controls.

It is interesting to surmise whether the toxæmia, as well as the megaloblastic anæmia, was induced by a deficiency of folic acid.

I wish to thank Dr. P. W. Dill-Russell, Director of Medical Services, for permission to publish these results, and Dr. M. Gosden, pathologist, for her assistance in the interpretation of the marrow biopsies.

Princess Margaret Hospital for Children, Perth, Western Australia. A. E. DUGDALE.

## ATHEROSCLEROSIS AND CORONARY (ISCHÆMIC) HEART-DISEASE

SIR,—In examining their own data for support for my suggestion [1] that the pathology of coronary heart-disease differs in middle-aged and old men, Professor Morris and Dr. Crawford (Jan. 7) overlook two relevant differences between their material and mine.

First, and more important, the age-structure of my sample was as follows:

| *Age (yr.)* | *No. in sample* | *Actual attendance* | |
|---|---|---|---|
| | | *No.* | *%* |
| 65–69 | 92 | 82 | 89 |
| 70–74 | 100 | 86 | 86 |
| 75–79 | 40 | 29 | 72 |
| 80–85 | 35 | 24 | 71 |
| Total | 267 | 221 | 82 |

Thus more than half of this population of Dublin pensioners are significantly older than any of the men described in the National Necropsy Survey. Secondly, I have observed clinical characteristics in the living; the observations they cited were of necropsy appearances. Before yielding to their disagreement —mild though it is—I would like to know more of the post-mortem appearances in the large group of (really) old men, who suffer from angina pectoris or show electrocardiographic changes suggestive of myocardial ischæmia (40% of the Dublin sample). Many of these accept their incapacity and do not mention it to their doctor,[2 3] so a necropsy survey not preceded by a very thorough symptomatic review of each patient could not hope to establish the exact clinical syndrome which corresponds to the pathological findings. Such extra information, which may be available, would make a valuable addendum to the interesting work of Dr. Laurie and Dr. Woods (Jan. 14).

Dr. Robb-Smith [4] has drawn attention to the constancy of the death-rate, relative to the total, of those aged 65 and over, ascribed to "myocardial degeneration" (I.S.C. 422)—a constancy which has also been observed outside England and Wales.[5] He has very guardedly suggested that this is in keeping with my hypothesis. Turning to I.S.C. 420 ("coronary artery disease"), I believe that, even when full allowance is made for inaccurate death certificates, a very considerably increased incidence of coronary thrombosis in middle-aged men is the only reasonable explanation for the changing patterns of the mortality statistics both in these islands and elsewhere.[5] Since Professor Morris has shown—to my mind most convincingly—that the amount of coronary atheroma has not increased over the past 50 years, his differentiation between disease of the lumen (thrombosis) and disease of the wall (atheroma) is inescapable, as is the conclusion that there must have been a change in the intravascular coagulability of the blood (at least in the coronary circulation) in men between the ages of 40 and 65 years.

I feel, in fact, that the only real difference between my views and those Professor Morris has expressed in his recent letter and elsewhere is that, while I have tentatively suggested that the clinical manifestations of coronary heart-disease in its milder forms in old people as distinct from middle-aged can be caused by mural atheroma without significant disease of the lumen, he does not believe that this idea is justified on the present evidence.

My research, which was made possible by Messrs. Arthur Guinness (Dublin), was carried out in the department of social medicine, Trinity College, Dublin.

London School of Hygiene and Tropical Medicine, London, W.C.1. ROY M. ACHESON.

1. Acheson, R. M. *Lancet*, 1960, ii, 706.
2. Sheldon, J. H. The Social Medicine of Old Age. London, 1948.
3. Acheson, R. M., Acheson, E. D. *Brit. J. prev. soc. Med.* 1958, **12**, 147.
4. Robb-Smith, A. H. T. *Lancet*, 1960, ii, 1028.
5. Acheson, R. M., Thornton, E. H. *Brit. J. prev. soc. Med.* 1958, **12**, 82.

## DEPRESSION ASSOCIATED WITH ADDISONIAN ANÆMIA

SIR,—The following case of depression associated with addisonian anæmia is recorded because the mood change responded to a thymoleptic drug before treatment for the anæmia began.

A woman of 68 was admitted in coma due to a suicidal overdose of barbiturate. On regaining consciousness, she reported that for one month she had been feeling low-spirited with loss of interest in her usual activities, difficulty in concentration, anorexia, and insomnia; she was also readily exhausted. Her husband said that her previously lively and humorous nature was altered, and that she had undergone a similar illness five years previously which had spontaneously remitted after three months. Clinical examination showed no abnormality, the cerebrospinal fluid was normal, and the hæmoglobin level was 11·6 g. per 100 ml. Mentally, she was retarded and self-recriminatory. A diagnosis of endogenous depression was made. The patient insisted that her symptoms were due to anæmia, showing more insight than did her doctors at this stage.

Oral imipramine (' Tofranil ') was given, and the dose was rapidly raised to 200 mg. daily. Within five days her depression started to lift, and it continued to improve, so that after six weeks on imipramine the only symptoms attributable to a mood disturbance were insomnia and an occasional feeling of apprehensiveness. Her exhaustion was more prominent, however, and her anæmia was therefore investigated. The hæmoglobin was again 11·6 g. per 100 ml., without macrocytosis; the serum-$B_{12}$ level was 90 μμg. per ml. (normal range 80–450), and a urinary diagnex blue test showed achlorhydria; marrow examination revealed occasional megaloblasts and a few giant metamyelocytes, indicating a mild vitamin-$B_{12}$ deficiency. She is now having this vitamin intramuscularly.

Presumably her predisposition to depression (as shown by the mood change five years previously) reacted with her shortage of vitamin $B_{12}$ to produce a depressive syndrome in the absence of subacute combined degeneration of the cord or optic atrophy. The improvement of the depression with imipramine alone is interesting, for neither the mode or action of this drug nor the exact way in which vitamin $B_{12}$ affects the nervous system are known. This case suggests that the two substances may act in related ways on the biochemistry of the brain.

Liverpool Royal Infirmary. J. S. MADDEN.

## SIR JAMES MACKENZIE, M.D., 1853–1925

Lord AMULREE writes:

"It has long been felt by his many admirers, not only in this country, but in America and on the Continent, that a new and more exhaustive biography of my uncle, Sir James Mackenzie, should now be written. Prof. A. Mair, who holds the James Mackenzie chair of social medicine at St. Andrews University, has been approached and has kindly agreed to do so.

"Would anyone who may happen to have any letters or private documents (other than books or publications) in any way pertaining to Sir James Mackenzie, please communicate direct with Professor Mair, or with myself at University College Hospital, London, W.C.1?"

# Obituary

## ERIC BENJAMIN STRAUSS

M.A., D.M. Oxon., Hon. D.Sc. Frankfurt, F.R.C.P.

Dr. E. B. Strauss, consulting physician in psychological medicine to St. Bartholomew's Hospital, died in London on Jan. 11 at the age of 66.

He was born in London and was educated at Oundle and University College School. After leaving school he spent a year in business in Canada, but this made no appeal to him, and he came back to this country shortly before the 1914–18 war, in which he served as a combatant. He was nearly 25 when in 1919 he went up to New College, Oxford, to read languages with a view to entering the diplomatic service. Already, however, he was interested in the mind, and he was prepared to hypnotise his fellow undergraduates. Within a few months he had decided to become a doctor, and he qualified from King's College Hospital in 1924.

He did not at once enter psychiatry. An appointment as medical registrar at the Maida Vale Hospital gave him a basic training in neurology which was to be of great value to him later, and led to his collaboration with Sir Russell Brain in the authorship of *Recent Advances in Neurology*, first published in 1929. But no opening appeared in neurology, and Strauss obtained a post at the Cassel Hospital for Functional Nervous Disorders, where Ross was then in charge. There Strauss had experience of a wide range of psychiatric problems, and learnt and practised an eclectic type of psychotherapy. If he was to become a psychiatrist, however, he needed more experience of the psychoses, so he worked for nine months with Kretschmer at Marburg. The Continental system reinforced in his mind the close links between neurology and psychiatry, and he was influenced by Kretschmer's special interest in the relation between physique, character, and mental disorder. At that time he translated into English Kretschmer's *Textbook of Medical Psychology*. His training thus completed, he was appointed physician in psychological medicine at St. Bartholomew's Hospital, and in the years before the late war he was a pioneer in the introduction of electrical convulsant therapy, or electroplexy, as he preferred to call it, into this country.

He also held appointments at the North Middlesex Hospital, St. Andrew's Hospital, Dollis Hill, and he was an external examiner for the National University of Ireland. In 1939 he was elected F.R.C.P. He gave the Croonian lectures in 1952 and was long secretary of the college's psychological medicine committee.

The following tributes from friends and colleagues who touched his life at different points show how much Strauss achieved and how much affection he won in doing so.

" Strauss's arrival at Barts in my student days was an event of some significance. He at once reorganised his department and admitted students for the first time to the outpatient clinics. Not only did he welcome us but he allowed some of us to talk to patients, so that their progress could be observed. He had considerable charm, a rich soothing voice, and a quiet playful sense of humour. He looked distinguished, especially when supporting his familiar monocle. His first course of lectures were brilliant and most stimulating and did much to whet one's appetite for more. How well one recalls his famous allusion to the mind as a mental iceberg, one-ninth showing above the surface, and his classic dictum: ' Psychiatry is the other half of medicine '. It was a step of some moment when he was allowed beds in certain medical wards—an innovation that may well have caused some elevation of eyebrows at the time."

J. B. G. S.

" Eric Strauss had left the Cassel Hospital shortly before I arrived in 1934. His personality was very much in evidence and it was already clear that he was going far. It was long before we had electro-shock, tranquillisers, or the numerous drugs of today to help us. Psychotherapy and sedation were the only available methods of treatment. Diagnosis was important to distinguish the early schizophrenic or the potentially suicidal depressive, and Strauss had already laid the foundation for his great reputation as a diagnostician. Inheriting certain patients who had been under him, I learnt much from his dealings with them. His psychotherapy was always based on common sense, and eclectic with no uncritical adherence to any one school. He was never afraid of a warm and human relationship with his patients, but always avoided or worked through any crippling transference, leaving the patient in command of himself and his own soul. It was sad that in Strauss's subsequent busy career his gift for psychotherapy had to be laid aside. It was characteristic of his kindliness and courtesy that, junior and unknown as I was, he called on me soon after I arrived; and I was amazed to find what a very approachable and friendly person he was, delighting in the country and simple things and absolutely free from pomposity."

M. G.

" Those of us who knew and worked with Dr. Strauss away from his teaching hospital saw perhaps a different and more informal aspect of his personality, and were impressed by a wide outlook and interest in his own specialty which might not have been so obvious to others. We who collaborated with him knew that there was a real and deep interest in the organic approach to psychiatry, and that his knowledge of this side of his work was as exceptional as his other interests.

" I think, however, that though his writings, so characterised by a practical common-sense point of view, will remain of importance for some considerable time, he will best be remembered for a warm and kindly personality which has been of inestimable encouragement and help to the fashioning of the careers of many with whom he came in contact, and whose influence was so generously given in an unobtrusive way. Lately, on a visit to Germany, I heard Professor Mall describe him as a friendly and wise guide. It is difficult to better this description."

J. C. B.

" Eric Strauss was a man of great culture, a good linguist, and a good musician. His training as a psychiatrist was based on the work of Kretschmer, for whom he had an immense admiration. Subsequently he built for himself a great reputation of his own, not only in this country but perhaps even more internationally. He was an excellent teacher and always encouraged the young. The students liked him and made him president of the Students' Union at Barts for two successive years. Always kind and always ready to help, Strauss, who was a truly religious man, had in abundance the greatest of the virtues, charity. It is hard to lose this colourful man who had the affection of us all."

E. R. C.

" Both his training and his temperament led Strauss to adopt a holistic approach to psychiatry. He stressed ' the principle of multiple causality ', which meant that in his view any psychological disorder should be considered in terms of psychic, somatic, constitutional and genetic, and social and environmental causal factors. Though he did not doubt the value of many of Freud's ideas he criticised Freud, and still more Freudians, for what he termed their ' heresy ' of undue emphasis upon psychogenesis to the exclusion of the other causes of mental disorder, and he had no sympathy with the philosophical and ethical views often associated with Freudianism. He brought to psychiatry an acute and critical mind, and a considerable

knowledge of psychology and philosophy, and philosophical criticism of psychiatry was to be the main theme of his presidential addresses to various psychiatric bodies and his Croonian lectures to the Royal College of Physicians. He was also much concerned about the place of psychiatry in medical education, and, as secretary for many years of the psychological medicine committee of the College, he constantly sought to bring the needs of psychiatry before it. He was not temperamentally inclined to research, and would have wished no better professional epitaph than that he lived up to the title of his appointment as 'physician in psychological medicine'.

"But those who knew Strauss only as a doctor knew only the smaller part of him. He was a sensitive man, and felt personally deeply involved in the tragedies, conflicts, and mounting tensions of the past thirty years. When the war was over he went to Germany to lecture on psychiatric subjects, and it gave him great pleasure when on his 60th birthday Frankfurt University conferred on him an honorary D.SC. His views on human nature were fundamentally Thomistic and he rendered a valuable service by interpreting and criticising current medical psychology in essays and reviews in Roman Catholic journals, especially *The Month* and *Blackfriars*.

"His wide knowledge of literature and the arts brought him into touch with many writers and artists. He not only enjoyed listening to music, but recently had made a gramophone record of piano pieces and songs he had composed. He was witty and humorous, and a generous host. Few men can have had more friends or kept in touch with them so well over the years. Unmarried himself, he was often a godfather to his friends' children, and in many families became a kind of universal uncle. Many people of all sorts and conditions, of all creeds and none, will find the world a colder place without Eric Strauss."

W. R. B.

## ARTHUR EATON RICHMOND

C.B.E., M.R.C.S., D.P.H., D.T.M.

AFTER Brigadier Richmond retired from the Army Medical Services, where from 1945 to 1949 he was Director of Army Health, he joined the staff of the Ministry of Health, and in his new appointment he continued his valuable contribution to preventive medicine and epidemiology. He died on Jan. 9 at his home in Sussex at the age of 68.

He was the son of the late Richard Richmond, M.D., and he was educated at Oundle School. He qualified from St. Thomas's Hospital in 1915; and the same year he was commissioned in the R.A.M.C., in which until 1919 he served in the Middle East and Egypt. The years between the wars he spent in India and the United Kingdom, and his interests turned to preventive medicine and hygiene. With McCombie Young and Brendish he studied sand-flies and sand-fly fevers in the Peshawar district, and he also published investigations on carbon-monoxide poisoning.

At the beginning of the late war he was assistant professor of hygiene at the Royal Army Medical College, and later he became in turn deputy director of hygiene in Eastern Command and of the Middle East Force. In 1945 he was appointed C.B.E., and the following year he returned to this country to become Director of Army Health at the War Office. He was awarded the Chadwick prize in 1950 and chose as the subject of his lectures the health of Middle East Forces. Of Richmond's special contribution to Army medicine A. E. C. writes:

"Richmond had been early impressed by the ideas of Ryle of Oxford, and the concept of positive health became part of his creed. Here was the impetus to carry the Army's older doctrines in the maintenance of health and prevention of disease to greater success, and from the Army into the community at large. His missionary spirit also found expression in his support of personnel research in the Army. He, like his predecessor at the War Office, felt the need for more study of the soldier in relation to the tasks being given him. During his tenure of office Richmond officiated at the birth of the PULHEEMS system of classification. Positive health, personnel research, and PULHEEMS—with these he may be said to have graduated Army Hygiene to Army Health. There will be those who will not agree with this change, but many will remember Richmond for his sincerity and enthusiasm, and the influence of his thought and character."

In 1950 after his retirement from the Army Medical Services Richmond became a temporary medical officer at the Ministry of Health. With his background and experience he was a valued link with the Service departments, but his most important work was done as secretary of expert committees on dysentery and influenza vaccine. Of his contribution to the M.R.C. Committee on Clinical Trials of Influenza Vaccine, C. H. S.-H. writes:

"To this task Richmond brought many years of experience of field work in the Army and he organised the complicated pattern of the field trials held under the auspices of the committee with superb skill. It is not too much to say that without Richmond's energy and enthusiasm these field trials might never have been held. His ability to gain the confidence of the many doctors concerned and to extract from them the necessary reports was an important asset which was vital to the success of the trials. He overcame many disappointments and frustrations and never lost sight of the end in view—namely, the proper statistical evaluation of the records. After some years of hard work with little reward he had the pleasure of collecting the evidence in 1957 during the extensive epidemic of Asian influenza which gave abundant proof of the value of influenza virus vaccine. His enforced retirement through ill health left a gap which was difficult to fill and it is sad that he had so short a time to enjoy the rest which he had earned so well."

A. T. R. also writes of Richmond's years at the Ministry:

"The wealth of knowledge and maturity of judgment which he brought to bear on any problem in preventive medicine, however difficult, proved of incomparable value. The standard which he set for himself in his daily work was of the highest order. Conscientiously and unquestioningly he applied his energies to the task in hand, and the discipline which so clearly governed his own conduct was reflected in the behaviour of all who came under the spell of his beneficent influence. Of his numerous activities, both inside and outside the Ministry, one that was probably nearest to his heart was his work on behalf of the Star and Garter Home, in which he took the keenest personal interest.

"With all his integrity of purpose, Richmond possessed a grand sense of fun. He combined dignity with good humour in proportions so well-balanced as to command equally the respect and affection of his colleagues. For me his most memorable characteristic will remain the feeling of cohesion and stability which he imparted to all his undertakings. Others may remember him more readily for his kindliness, generosity, and unfailing courtesy. In the ultimate, to use one of his own favourite phrases, we who knew that neat little figure, with the many endearing foibles and turns of speech, will think of Arthur Richmond as a man whose like we shall hardly see again."

D. T. describes the special place which Richmond won for himself among his colleagues at the Ministry:

"After a lifetime in the R.A.M.C., during which he had held several important commands in his specialty, the transition to a relatively minor position in civilian medicine must have been, for him, a sharp one. But he showed clearly that it was the man, rather than the rank, which matters. Soon his kindliness, cheerfulness, self-effacement, and uprightness of character, gained the respect and affection of his new colleagues. And, as the years went by, his quiet influence came to be held in increasing

regard. This applied not only to his contemporaries, but even more so in the case of those much younger than himself, with whom his daily lot was often cast. To them he was a guide and adviser of inestimable value, and they were ever eager to benefit from his wide experience, knowledge, and wisdom. They could not have wished for a more helpful mentor.

"A large Government department is not a place where it is easy for an individual to project his personality or to arouse the deeper beneficent emotions. It was a measure of Arthur Richmond that—amply endowed as he was with what Osler called 'the incorruptible treasures of the heart'—in the Ministry of Health he was held in affectionate esteem by all who knew him."

Brigadier Richmond married in 1916 Miss Margaret Kelly of Tuam, Galway, and she survives him with one son.

## DONALD BAGSTER WILSON

O.B.E., M.D. Cantab., M.R.C.P., D.T.M. & H.

Dr. D. Bagster Wilson, formerly director of the East African Institute of Malaria and Vector-borne Diseases, died on Dec. 29 at the age of 59, only a few months after he had retired from the East African Medical Service.

He was educated at Monkton Combe School, St. Catherine's College, Cambridge, and the Birmingham Medical School. He qualified in 1926 and took the D.T.M. & H. in 1929. The same year he joined the East African Medical Service.

In 1932 he took charge of the newly constituted malaria unit at Tanga. This was the beginning of the series of investigations on malaria and its control which were to occupy the rest of his professional career. In this work he was ably assisted by his wife, herself a distinguished parasitologist. Their intensive researches on hyperendemic malaria in African villages, in which observations were recorded on individual subjects as they passed through various stages of parasitic infestation from infancy onwards until partial or complete immunity was attained, were comparable with similar studies by Schuffner in the Dutch East Indies and Christophers in India.

In the late war Wilson joined the Army, where he was appointed to a malaria unit and attained the rank of lieut.-colonel, serving in Madagascar, Ethiopia, and other parts of Africa. After the war he continued his work on malaria and in 1949 was appointed officer in charge of an East African malaria unit at Muheza near Tanga. This unit was later expanded to become the East African Institute of Malaria and Vector-borne Diseases, with headquarters at Amani, in the Usambara hills 20 miles north of Muheza. Wilson devoted an immense amount of labour to the building up of this institute, which became a centre of research, training, and consultative work on malaria and other vector-borne diseases, including schistosomiasis. After ten years as director he retired in 1959. He was appointed O.B.E. in 1953.

G. C. writes:

"My own association with the Wilsons dates from 1934, when they visited India on a study tour. In later years I stayed with them on a number of occasions in their charming home at Amani, of which I have the most pleasant recollections. Wilson was a man of high principles and forceful character, with immense energy and drive. His epidemiological studies led him to advocate caution in the application of measures which might disturb the high degree of immunity acquired by the indigenous inhabitants of tropical Africa as the result of repeated reinfection. He was a charming host with a great sense of humour and a lively appreciation of the good things of life, and will be greatly missed by his many friends, both in East Africa and in this country."

E. R. C. writes:

"Donald Bagster Wilson was a man of passionate sincerity. He hated superficial or careless thinking as greatly as he despised humbug and pomposity. His intense studies were carried on throughout the war far and wide over Africa and islands in the Indian Ocean right up to his recent retirement to Wiltshire from his lovely home in Amani in Tanganyika, the site of the old German arboretum. At the time of his death he was writing a book on his wide experiences in malaria. Wilson was a lovable, interesting, and entertaining man who will be sadly missed by his many friends who so admired him."

In 1932 Dr. Bagster Wilson married Dr. Margaret Elizabeth Lovett. She survives him with their two daughters.

## THOMAS HERBERT OLIVER

M.A. Cantab., M.D. Manc., F.R.C.P.

Dr. T. H. Oliver, emeritus professor in the University of Manchester, died at his home in Sidmouth on Jan. 12. Essentially a general physician with a special interest in diabetes, he took a great part in setting up a department of dietetics at Manchester Royal Infirmary.

He came to Manchester in 1909 as an entrance scholar in medicine from Caius College, Cambridge, where he was placed in the first class of the natural sciences tripos. He qualified with honours in the Manchester M.B. in 1912 and took his M.D. degree seven years later. During the 1914–18 war he served in the R.A.M.C. in Mesopotamia.

Shortly after demobilisation he was appointed assistant physician to the Manchester Royal Infirmary and in due course was promoted physician. In 1931 he was elected F.R.C.P. For many years he was clinical dean of the Manchester Royal Infirmary and physician-in-charge of the department of dietetics which he had helped to found. During the late war he was part-time professor of clinical medicine; and in 1944, when a full-time professor was appointed, a new chair of therapeutics was established for him in recognition of his services to the university.

Oliver was president of both the Manchester Medical and the Manchester Pathological Societies, and was an examiner at Cambridge University in medicine and therapeutics.

His twin hobbies were Continental travel and colour photography. This, in his later years, led to his being in considerable demand as a popular lecturer.

C. B. writes:

"I had the good fortune to enjoy the friendship of Tommy Oliver for over half a century and to work in double-harness with him when we were clinical and systematic professors of medicine in Manchester during the late war. One could not possibly have wished for a more congenial colleague; for, though he held strong opinions, and was prepared to defend them, he always gave courteous consideration to the views of others and adopted a statesmanlike attitude in committees.

"He could not abide sham or pomposity. After the 1914–18 war we were in digs together until the time of his marriage and, even in those days, his friends and contemporaries treated him with the respect due to a man of much more mature years. This earned him the title of 'Uncle Tom'.

"He set himself a very high standard and never deviated from it. This applied not only to his clinical work and his teaching, but also to his favourite hobby—colour photography. The beautiful pictures taken on his Continental holidays gave much pleasure to his friends as well as to wider audiences.

"Oliver will be remembered not only as a first-class physician, but also as a great gentleman."

Professor Oliver leaves a widow and one daughter who is married to the professor of surgery in Adelaide.

# Notes and News

## TURKISH HEALTH SERVICE SCHEME

THE Turkish National Unity Committee (*Times*, Jan. 11, 1961) have announced that it is proposed to set up a health service in Turkey. A few months ago Dr. Daniel Thomson, a deputy chief medical officer of the Ministry of Health, visited Ankara and gave a lecture on the National Health Service, and it is understood that plans for the new Turkish service will be based on the N.H.S.

The basic unit of the service is to be a "health house", and 27,000, each catering for 25,000 people, are to be set up in Turkey's 40,000 villages. Small health centres will deal with 5000–10,000 people and larger ones, with twenty-five to one hundred beds, with 50,000–100,000 people. Regional hospitals of four hundred beds will serve populations of 150,000 people. Drugs costing up to £1 will be free to everyone. Contributions will cost each family about £1 a year.

The scheme is to be tried in three pilot zones and over the next fifteen years extended to the whole country.

## EDINBURGH ROYAL INFIRMARY

PLANS for rebuilding Edinburgh Royal Infirmary were announced on Jan. 13.[1]

Prof. Robert Matthew, professor of architecture at Edinburgh University, and Prof. Llewelyn Davies, professor of architecture at London University, cooperated in producing an outline scheme. 5 buildings in the central area, including a nurses' home, could be demolished first. The new boiler-house would then be built; and then a 12-storey ward block, facing the Meadows, and the teaching accommodation. Thereafter the rest of the old hospital would be demolished. The purpose of this staged scheme was to ensure that the hospital ran smoothly while rebuilding proceeded. There were to be 800 beds—300 fewer than at present. The cost would be between £7 and £9 million; and the scheme would take six years to complete.

Other features would be: a garage for 600 cars; a tunnel from the university buildings in George Square; and space for the Sick Children's Hospital, to be built later. The Florence Nightingale Nurses' Home and the Simpson Memorial Maternity Pavilion would be retained.

Mr. J. S. Maclay, Secretary of State for Scotland, emphasised that detailed plans and timing still had to be worked out. He envisaged two major teaching hospitals in Edinburgh, the other being the Western General, with 1500 beds between them.

## RADIOACTIVE UNSATURATED FATTY ACIDS

MUCH of the evidence about the relation between coronary-artery disease and saturated fatty acids in the diet is conflicting, and a convenient source of "labelled" unsaturated fatty acids is essential for further research. The freshwater alga Chlorella produces a range of unsaturated acids, and is easy to grow in the laboratory.

At the Radiochemical Centre at Amersham, Chlorella is grown under sterile conditions in an atmosphere of radioactive carbon dioxide. Because the organism has access to no carbon other than that from the radioactive gas, all the acids it evolves are radioactive.

Batches of radioactive Chlorella can be grown in one to two weeks, but the extraction and separation of the unsaturated acids takes two to three months.

The tough skin of the organism is split by ultrasonic methods; this is followed by centrifugation and freeze-drying. The final separation of the unsaturated acids is done by paper chromatography.

Because of the world-wide demand for labelled fatty acids, the United Kingdom Atomic Energy Authority is seeking ways of simplifying the present complex laboratory techniques.[2]

## TREATMENT OF CASUALTIES

THE Ambroise Paré Surgical Club spent the morning of Jan. 14 in a way their patron would surely have enjoyed—seeing the latest in military surgery. After a clinical meeting at the Queen Alexandra Military Hospital, Millbank, the club adjourned to the barrack square of the Royal Army Medical College, where modern training in the early treatment of casualties was vividly demonstrated. After a new F.N. rifle has been fired a soldier appeared to have been shot in the forearm. His sleeve was swiftly cut open, exposing a realistic wound. The patient was given morphine and antibiotics from plastic ampoules attached to sterile needles. The first field dressing was rapidly applied to the wound and the limb was immobilised above and below the injury with a plaster slab. This slab of quick-drying plaster had fringes of gauze along its length, so that it could be speedily moulded around the limb. The wounded man was treated and ready for evacuation seven minutes from the original injury.

The meeting ended with a film and a talk on mouth-to-mouth and mouth-to-nose resuscitation, a method which is acknowledged to have superseded previous techniques of artificial respiration. At the end of his talk, the anæsthetist fell down apparently electrocuted, but he was promptly revived by a staff-sergeant who had clearly been well trained in the new method.

1. *Scotsman*, Jan. 14, 1961.
2. *Electron Whly*, Jan. 11, 1961, p. 3.

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### University of Oxford

The United States Public Health Service has given a grant of $70,000 for five years, ending Sept. 30, 1965, for research on a survey approach to problems of cancer prevalence, which is to be carried out in the social medicine unit under the direction of Dr. Alice Stewart.

### University of Cambridge

A course on metabolic disorders in clinical medicine, arranged by Prof. R. A. McCance, will be held from April 10 to 12. Registration forms may be had from the secretary, Medical School, Tennis Court Road, Cambridge. The course fee will be £5 5*s*.

### University of London

Dr. E. F. Scowen, reader in medicine at St. Bartholomew's Hospital Medical College, has been appointed to the university chair of medicine at the college.

Dr. Scowen, who is fifty years of age, was educated at the City of London School and St. Bartholomew's Medical College, graduating M.B. Lond. in 1932. After holding house-posts there he joined the medical professorial unit in 1934 as second assistant. He later became first assistant and in 1937 became assistant director of the unit and assistant physician to the hospital. The same year he was granted leave of absence to take up a Rockefeller Foundation scholarship at the University of Columbia, New York, with Dr. Philip Smith. He was appointed physician at St. Bartholomew's Hospital in 1945 and director of the medical professorial unit in 1955. In 1941 he was elected F.R.C.P. and in 1960 F.R.C.S. His published work includes papers on endocrinology, metabolism, and cancer.

The title of reader in medicine has been conferred on Dr. P. H. Sanderson in respect of his post at St. Mary's Hospital Medical School.

### University of Bristol

The degree of M.D. has been conferred on M. S. Dunnill.

### University of Sheffield

A course dealing with psychiatric problems arising in general practice will be held on March 25 and 26 at the Whiteley Wood Clinic, Sheffield. Further details will be found in our advertisement columns.

### University of Glasgow

On Jan. 14 the following degrees were conferred:

*M.D.*—J. E. Lunn, E. J. R. Primrose (with commendation); J. M. Wallace.

*M.B., Ch.B.*—Eugene Ifeanyichukwu Akwule, Archibald Alexander, Liadi Alabi Alli-Balogun, Freda Berry, J. M. Blaikie, Akinsanya Borokini-Dada, D. M. Brown, C. C. A. Campbell, Stuart Campbell, Alexander Clark, A. M. Clark, J. W. H. Crosbie, Jessie S. Cubie, J. J. Fitzpatrick, G. G. Forrest, R. C. Gibson, John Kerr, Evelyne M. E. Laidlaw, G. D. Lewis, C. A. P. Maley, Patricia M. Menzies, John Nicol, Irene F. D. Patterson, J. G. R. Robertson, A. P. Robinson, Marion E. Russell, Som Datt Karamchand Soni, I. D. Walters.

### Queen's University, Belfast

At graduation ceremonies in July the honorary degree of LL.D. will be conferred on Sir David Campbell and of D.SC. on Prof. J. Dixon Boyd.

### National University of Ireland

At a meeting on Jan. 12 M. F. Murnaghan was granted the degree of M.D.

### Royal College of Surgeons of England

At a meeting of the council on Jan. 12, with Sir Arthur Porritt, the president, in the chair, Lieut.-Colonel J. C. Watts was admitted as the joint professor of military surgery in the Royal Army Medical College and the Royal College of Surgeons.

Mr. G. T. Hankey was presented with the John Tomes prize for 1957–59. Dr. Margaret A. Branthwaite and Dr. A. Garendran were awarded the Nuffield prizes for anæsthetics.

Mr. W. Gissane was appointed the Robert Jones lecturer, and Dr. G. S. W. Organe Joseph Clover lecturer for 1962. Dr. Frank Stansfield was reappointed Bland-Sutton lecturer for 1960–63.

A diploma of fellowship was granted to G. V. Shead; and of membership to E. S. Marsden. The following diplomas were granted jointly with the Royal College of Physicians:

*D.L.O.*—John Atkins, M. J. Boyle, W. G. Edwards, K. P. Ferris, Balraj Singh Gill, H. J. Griffiths, C. P. Gyaw, Syed Wahaj-ul Hasnain, A. V. Hayes, Suhail Rasheed Hilmi, Maung San Hla, J. M. Jackson, S. C. Jayarajah, Mohan Ganesh Jog, M. R. Landeg, Kayyalakakathu Mathen Mathen, T. M. O. Morris, D. R. Owen, Vaitilingam Ramachandra, Hlaing Thar, W. N. Tucker, D. S. Wijeyaratne, I. I. Wilson, R. A. Yorston.

*D.A.*—Nasir Ahmad, P. C. Anderson, Mary E. Ashworth, Ritabrata Basu, E. F. Battersby, D. de G. Binns, Joyce Bourne, D. J. Bowen, C. R. Brown, Barbara J. Burbridge, Muhammed Zubair Butt, R. A. Cahi, Jill M. Cary, Sudhirendra Lal Chanda, Jayantilal Mohanlal Chokashi, G. E. Clews, Rosemary M. Coffey, David Cohen, W. G. Conn, J. H. Croft, Andrew Cunningham, J. S. Davis, D. E. Day, A. V. Dreosti, Christine P. Elgood, T. L. Fraser, Elizabeth P. Gibbs, S. D. Giddy, R. T. Glen, R. W. Griffin, P. B. Hardwick, W. R. Heaton, W. R. Hesson, Margaret A. Hickey, A. L. Hovenden, T. A. Hussell, Marjory M. R. Jukes, Q. L. D. Kalpage, Sheila Keswani, K. L. King, Anna W. Koeller, Audrey M. Lake, R. W. Lamb, R. A. Lea, E. G. Leonard, T. C. McAslan, D. J. F. Macdonald, Roma McDonald, R. C. Macfarlane, Jacque Gaillard Mar, Annabel J. M. Mason, Nalini Vinodrai Mehta, Jean Moffatt, K. M. Moore, A. B. Mulholland, C. W. A. Murray, Jennifer L. Murray, Unnati Sundri Mushran, Muthu Navaneetham, B. J. O'Neil, Nalin Paymaster, R. K. Pears, Eve M. Pitt, D. A. Pottinger, Valerie J. Prior, L. R. Redman, Marion E. Richardson, Thomas Riley, Jean M. Ritchie, D. G. L. K. Russell, Dolly T. Salami, Felicity H. Sambrook, W. J. W. Siddall, John Southern, E. B. Steffenssen, Pamela M. Stracey, A. G. Tetlow, Gaynor Thomas, H. R. Turner, U Tin Maung, J. F. Viljoen, J. D. Villiers, K. P. Wilson, R. C. Young.

*D.M.R.D.*—Kamla Bery, W. A. Brown, Victor Cope, J. D. Craven, J. S. H. Davidson, J. A. Gleeson, J. H. Highman, Wei-Yik Paul Huang, W. A. John, Akram Makki Kasem, J. P. Lavender, K. W. Lavers, Leila Liebster, Mary B. B. McGregor, Mohammad Ali Mehran, H. L. Miller, M. A. B. Ogakwu, B. W. Petty, Vallury Venkateswara Surya Pratapa Rao, J. H. Roberts, E. J. Roebuck, H. W. P. Rooke, Sakti Prasad Sarkar, H. H. Shawdon, Jaswant Singh Sodhi, U Ko Ko, J. M. Welchman, F. R. Wright, Sahib Baker Zainy.

*D.M.R.T.*—Joan W. Baker, Pui-Sek Daniel Chan, N. C. N. Cooray, William Duncan, N. V. Hawkins, D. J. Mahy, J. A. G. Matthews, Maung Mya Thin, Munir Ahmed Siddiqui, Jean F. Staffurth, Anam Sudarsanam, I. D. H. Todd.

*D.P.M.*—W. D. Addis, J. E. Barclay, Laurance Barclay, Ashutosh Bhattacharya, W. D. Boyd, P. K. Bridges, Purushottam B. Buckshey, Nani Gopal Chakraborty, Joan R. Christison, Norman Crook, M. H. De Groot, J. A. Dew-Jones, G. O. Dubourg, Donald Eccleston, Mounir Ekdawi, B. H. Fookes, P. L. G. Gallwey, B. M. Groden, Peter Hall, Patrick Harper, I. N. S. Heald, J. H. Henderson, R. N. Herrington, H. M. Holden, J. A. Ireland, T. E. Lear, Veronica H. Longman, E. C. MacLeod, D. H. Marjot, Jerzy Mieczyslaw Mielczarek, G. M. J. Nicholl, J. H. Padel, Ramaswami Padmasini, T. A. A. Pearce, F. C. S. Pearson, J. D. Pryce, Ronald Seymour-Shove, M. S. Spelman, Onkar Nath Srivastava, J. A. Stewart, Kenneth Stewart, J. D. Stirland, J. R. Unwin, J. J. Waldron, C. B. Whittaker, D. H. Yates.

*D.Path.*—J. D. Barrie, E. C. Christian, Roger Gillett, Alice B. E. Gray, Beryl Jameson, Bodh Krishna Jha, J. R. Rawstron, Kishwar Zahur-ud-Din.

*D.P.H.*—Abul Hashem Akhand, Budhindra Chandra Bardalai, Mary K. Astin, M. A. Baddoo, J. R. F. Boger, Jean Buchanan, P. B. Cook, J. N. Docherty, J. A. Dryden, P. M. Fea, K. W. H. Fenwick, M. T. Fernandes, J. E. J. Hurman, R. G. Isaac, Shirley Jessop, H. H. John, D. T. Jones, Kirpal Singh Laungia, J. A. Moffitt, J. R. P. Murley, B. M. Nolan, R. M. Oliver, Phanindra Lal Ray, Pathew Sukavachana.

*D.T.M. & H.*—Akhtar Ali Ahmad, Anthony Coady, D. F. Conway, R. J. Givans, P. C. C. Pitt, Habibar Rahman, Madhukar Eknathrao Wable.

*D.I.H.*—George Groves.

*D.C.H.*—Shirley E. Willis.

### Royal Faculty of Physicians and Surgeons

At a meeting on Jan. 9, Dr. J. H. Wright, the president, in the chair, the following were admitted fellows of faculty *qua* surgeon:

R. S. Barclay, Gajanan Trimbak Bhopatkar, A. G. Hutchison, A. G. Kilcoyne, T. S. Mann, T. C. White.

### National Association for Maternal and Child Welfare

The annual conference of this Association will be held from June 28 to 30. Further particulars may be had from the secretary of the Association, Tavistock House North, Tavistock Square, London, W.C.1.

### Doris Odlum Prize

The British Medical Association announce that Dr. Doris Odlum has endowed a prize (£80) for research in mental health. It will be awarded for the first time in 1962 for a study of progress in the community care of mental disorder. Further particulars may be had from the secretary of the Association, B.M.A. House, Tavistock Square, London, W.C.1.

### Postgraduate Medical School of London

A symposium on selected topics in chemical pathology will be held from April 18 to 20 at the school, Ducane Road, London, W.12. The titles of the sessions will be magnesium metabolism, renal failure, serum enzymes, blocks in intermediary metabolism, and instrumentation. Applications to attend should be made by March 22 to the Dean at the school.

### International Symposium of Stereoencephalotomy

This symposium, organised by the Cerebral Stereotaxic Institute of Temple University, is to be held on Oct. 11 at the Temple University Medical Center, 3401, N. Broad Street, Philadelphia. Further particulars may be had from Dr. Henry T. Wycis at the Medical Center.

### A "Rubella" Parents' Group

A group which has been formed by parents of handicapped children whose mothers had rubella in the early months of their pregnancy have held a conference on children with a combined visual and auditory handicap. The conference met on Jan. 7 and 8 at Condover Hall School for Blind Children, where there is a special unit for these children, and it was attended by doctors, teachers of the deaf, workers in deaf and blind welfare, and health visitors and representatives of the Ministries of Health and Education and the Society of Medical Officers of Health. The secretary of the group is Mrs. Peggy Freeman of 63, Horn Lane, Woodford Green, Essex.

### New Scheme at Papworth

Papworth Village Settlement has now arranged with the Cambridgeshire welfare department to extend their scheme for handicapped people. Men and women who are not up to the required standard for the Ministry of Labour training scheme may now be admitted for permanent residence and sheltered occupation in the new workshop at the settlement.

The welfare department of the local authority of residence will pay £6 6s. per week for each person, less the handicapped person's contribution as assessed under the National Assistance Act, 1948. The settlement will transfer the handicapped person to the status of wage-earner, according to agreement with the trade unions, as soon as possible after admission. At this stage the charge of £6 6s. a week will cease, and the welfare department will be asked to supplement the Ministry of Labour deficiency grant up to a maximum of £135 per annum for each person admitted. Men and women up to the age of 45 (and over in exceptional circumstances) can be considered for admission. Applications should be sent to the secretary, Papworth Hall, Papworth Village Settlement, Cambridge.

### Preparation for Retirement Committee

This committee, with a grant from the National Old People's Welfare Council, have appointed a full-time officer to implement the recommendations made in their report, *Preparation for Retirement or Adjustment to Ageing*. They believe that special efforts should be directed to widening interests and contacts in the forties when the pressures of the family slacken, and to practical courses for those in their fifties. They are preparing a series of programmes which can be adapted for use by adult education centres, discussion groups, and conferences. The Glasgow Retirement Council already run day-release courses for people still in employment and craft and hobby centres for those who have retired, and the committee hope that with the cooperation of both sides of industry, the educational authorities, and voluntary organisations it will be possible to start more local councils. They also propose to issue a series of publications, of which the first three will be *Solving New Problems*, *Physical and Mental Health*, and *Finance and Living Arrangements*. Further particulars may be had from Miss L. M. Hubbard, N.O.P.W.C., 26, Bedford Square, London, W.C.1.

### College of Speech Therapists

This college is to hold a conference from July 24 to 28 in Birmingham. Further particulars may be had from the conference organising secretary, 16, York Road, Birmingham, 16.

### International Association of Gerontology

A meeting of the European clinical section of this Association will be held from Sept. 13 to 16 at The Hague, Netherlands. Further particulars may be had from Dr. E. Woodford-Williams, department of medicine and geriatric medicine, General Hospital, Chester Road, Sunderland.

### International Congress of Angiology

This congress, organised by the Union Internationale d'Angéiologie of Paris, is to be held from Sept. 4 to 9 in Prague, Czechoslovakia. Further particulars may be had from the secretary-general of the congress, Prof. Dr. Zdeněk Reiniš, IVth Medical Clinic, U nemocnice 2, Prague 2.

### Increase in Nurses' Salaries

Nurses and midwives employed in hospitals and by local authorities in the National Health Service will receive a salary increase of 5% under an agreement reached by the Nurses and Midwives Whitley Council. The increase dates from Dec. 1, 1960. Board and lodging charges will remain unchanged. Nurses' salaries were last increased on March 1, 1959.

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The health care division of the HYSPA exhibition, to be held in Berne from May 18 to July 17, is organising a competition for professional producers for a film on health care. Further particulars may be had from the division, Schauplatzgasse 23, Berne, Switzerland.

A semipermanent exhibition will be held at the Institute of Dermatology, Lisle Street, London, W.C.2, from Feb. 1 to 24, by Dr. K. V. Sanderson on seborrhœic warts.

CORRIGENDUM: *Humoral Changes in Arteriosclerosis.*—In the article by Prof. W. Schrade and his colleagues (*Lancet*, 1960, ii, 1409) the values of P should be preceded by the sign <, *not* >.

## Appointments

AGNEW, R. A. L., M.D. Dubl., M.R.C.P.I.: assistant chest physician, Chesterfield and North Derbyshire area.
BHANDARI, N. P., M.B. Lond., D.P.H.: deputy M.O.H., St. Pancras.
BRYANT, GILLIAN M., M.B. Wales, D.C.H., D.OBST.: assistant M.O.H. and school M.O., Newport, Mon.
DIGGLES, HARRY, M.B. Manc., D.P.H.: M.O.H., Northallerton, Aysgarth, Leyburn, and Masham.
DOYLE, J. O., M.D. N.U.I., M.R.C.P.I.: assistant venereologist to Newsham General Hospital and the Seamen's Dispensary.
GALBRAITH, JOYCE M., M.B. N.U.I., D.P.M.: assistant psychiatrist and deputy medical superintendent, Liverpool Hospital, Frodsham, Cheshire.
GEORGE, PHYLLIS A., M.B. Lond., F.R.C.S.: part-time consultant surgeon, Royal Free Hospital, London.
HADFIELD, IAN, B.M. Oxon., D.P.M.: consultant child psychiatrist, child-guidance clinics, Hampshire.
PAMPIGLIONE, GIUSEPPE, M.D. Rome, M.R.C.P.: part-time consultant, department of electroencephalography, Royal Free Hospital, London.
POLLITT, J. D., M.D. Lond., M.R.C.P., D.P.M.: physician, department of psychological medicine, St. Thomas's Hospital, London.
RANKINE, ROBERT, M.D. Glasg.: consultant geriatrician, Fife.
ROBERTS, D. P. W., M.B. Birm., D.OBST., D.P.H.: M.O.H., Rhyl and Prestatyn urban district, and St. Asaph rural district.
SHUTTLEWORTH, K. E. D., M.B. Lond., F.R.C.S.: genitourinary surgeon, St. Thomas's Hospital, London.
THOMAS, A. E., M.B. Manc., M.R.C.P.: consultant physician, Nottingham City Hospital.
THORPE, J. N., M.B. Edin., F.F.A. R.C.S., D.A.: consultant anæsthetist, Alton and Winchester hospital group.

**Western Regional Hospital Board, Scotland:**

BARR, G. T. D., M.B. Glasg., M.R.C.O.G., D.OBST.: consultant obstetrician and gynæcologist, Eastern District Hospital, Glasgow.
MACDONALD, H. R. F., M.D. Glasg., F.R.F.P.S.: consultant physician, Motherwell, Hamilton area with duties at Stonehouse and Cleland Hospitals.
MACLENNAN, H. R., M.D. Glasg., F.R.C.O.G., F.R.F.P.S.: consultant obstetrician, Royal Maternity Hospital, Glasgow.
MCCALL, J. K., M.B. Dubl., D.O.: assistant ophthalmologist, Glasgow Eye Infirmary.
MUNRO, J. R., M.B. Edin., F.F.A. R.C.S.: consultant anæsthetist, Royal Hospital for Sick Children, Glasgow.
MURDOCH, ROBIN, T.D., M.D. Glasg., F.R.F.P.S., M.R.C.O.G.: consultant gynæcologist, Royal Samaritan Hospital for Women, Glasgow.
SCOTT, L. S., M.B. Glasg., F.R.C.S.E., F.R.F.P.S.: consultant urologist, Western Infirmary, Glasgow.
TINDAL, ANDREW, M.B. Glasg., F.F.A. R.C.S., D.A.: consultant anæsthetist, Glasgow Dental Hospital and School.
WHITELAW, J. W., M.B. Glasg.: consultant pathologist (hæmatology), Southern General Hospital, Glasgow.

## Diary of the Week

JAN. 22 TO 28

### Monday, 23rd

UNIVERSITY OF LONDON
6 P.M. (Birkbeck College, Malet Street, W.C.1.) Dr. Simon Biesheuve (Johannesburg): Problems of Cross-cultural Ability Testing.
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. W. T. Cooke: Regional Enteritis.
HUNTERIAN SOCIETY
8.30 P.M. (Guildhall, E.C.2.) Prof. Fritz Linder: Surgery in Germany, with Special Reference to Pulmonary Lesions.
UNIVERSITY OF LIVERPOOL
5.15 P.M. (New Medical School.) Prof. D. E. Paterson (Madras): Radiological Manifestations and Sociological Aspects of Leprosy.
MANCHESTER MEDICAL SOCIETY
5 P.M. (Dental Hospital.) *Odontology.* Dr. Aron Holzel: Allergy.
9 P.M. (Medical School.) *General Practice.* Dr. L. A. Liversedge: Fact and Fancy in the Treatment of Multiple Sclerosis.

### Tuesday, 24th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Medicine.* Dr. A. M. Dawson, Dr. R. S. Williams, Dr. C. F. Hawkins, Dr. B. E. C. Nordin: Metabolic Disorders in Gastro-intestinal Disease.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. Gilbert Causey: Structure and Function of the Supporting Tissue of the Nervous System.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. K. V. Sanderson: Epithelial Tumours.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Dr. Erica Wachtel: Cancer Diagnosis by Vaginal Cytology.
SOCIETY FOR THE STUDY OF ADDICTION
8 P.M. (11, Chandos Street, W.1.) Prof. G. C. Drew: Effect of Small Doses of Alcohol on Skills.
MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School.) Prof. J. E. C. T. White: Discovery of Man. (University lecture.)

### Wednesday, 25th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Professor Causey: Appreciation of the Fine Structures of Some of John Hunter's Specimens. (Arnott demonstration.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. H. E. M. Kay: Realities of Bone Marrow Transplantation.
ROYAL SOCIETY OF MEDICINE
5 P.M. *Endocrinology.* Prof. C. E. Dent, Prof. F. T. G. Prunty, Dr. Nordin, Dr. Mary McGeown: Diagnosis of Hyperparathyroidism.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Y. M. Clayton: Fungi Causing the Mycotic Diseases.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. J. G. Scadding: Effect of Corticosteroids in Tuberculosis.
ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Dr. D. A. J. Tyrrell: Common Cold Problem.
UNIVERSITY OF OXFORD
5 P.M. (Radcliffe Infirmary, Oxford.) Sir John Peel: Diabetes in Pregnancy. (Litchfield lecture.)

### Thursday, 26th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr. N. G. Rothnie: Changes in Blood Coagulation due to Perfusion for Open Heart Surgery. (Arris and Gale lecture.)
UNIVERSITY OF LONDON
5.30 P.M. (London Hospital Medical College, Turner Street, E.1.) Dr. F. C. Fraser: Adaptations in Cetaceans.
5.30 P.M. (School of Pharmacy, 29, Brunswick Square, W.C.1.) Prof. T. Vályi-Nagy (Debrecen): Pharmacology of Antibiotics. (First of two lectures.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. W. V. Mayneord: Radioactivity of the Human Environment.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Mr. A. J. King: Skin Manifestations of Treponematoses.
WEST LONDON MEDICO-CHIRURGICAL SOCIETY
8 P.M. (Rembrandt Hotel, S.W.7.) Rev. Maurice Bell: Social Upheavals in Western South America.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Queen's College, Dundee.) Dr. E. J. Ross: Aldosterone.

### Friday, 27th

UNIVERSITY OF LONDON
5.30 P.M. (School of Pharmacy.) Professor Vályi-Nagy: Pharmacology of Antibiotics. (Second of two lectures.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. S. M. Cohen: Limb Gangrene.
4 P.M. Dr. Stanley Bell: Management of Malaria.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Dr. T. V. L. Crichlow: Cholesteatoma and Mastoid Disease.
MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, W.1
7.30 P.M. Dr. Robert Lees, Mr. King: Future of Venereology.
MIDLAND CENTRE FOR NEUROSURGERY, Holly Lane, Smethwick, Birmingham
8 P.M. Dr. W. Ritchie Russell: Aphasia.

### Saturday, 28th

BRITISH ASSOCIATION OF ALLERGISTS
11 A.M. (1, Wimpole Street, London, W.1.) Short papers.
2 P.M. Symposium on Farmer's Lung.